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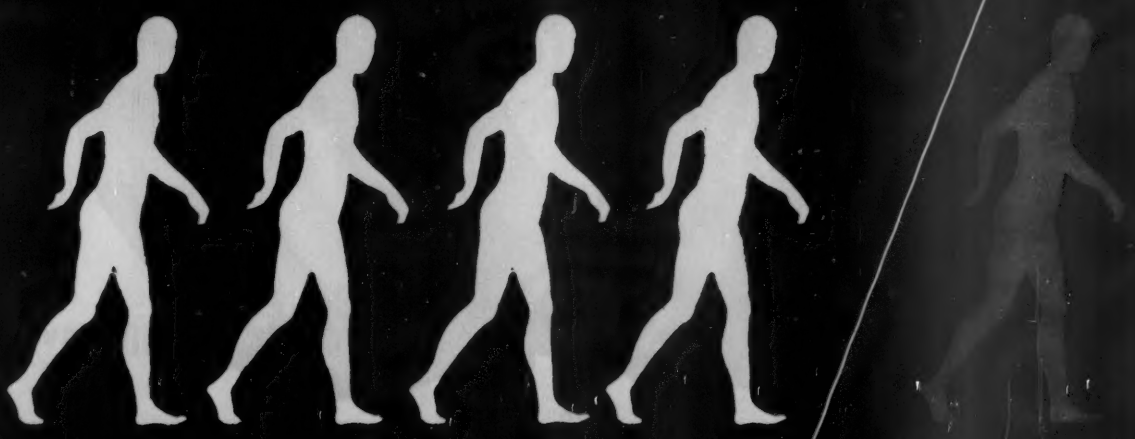

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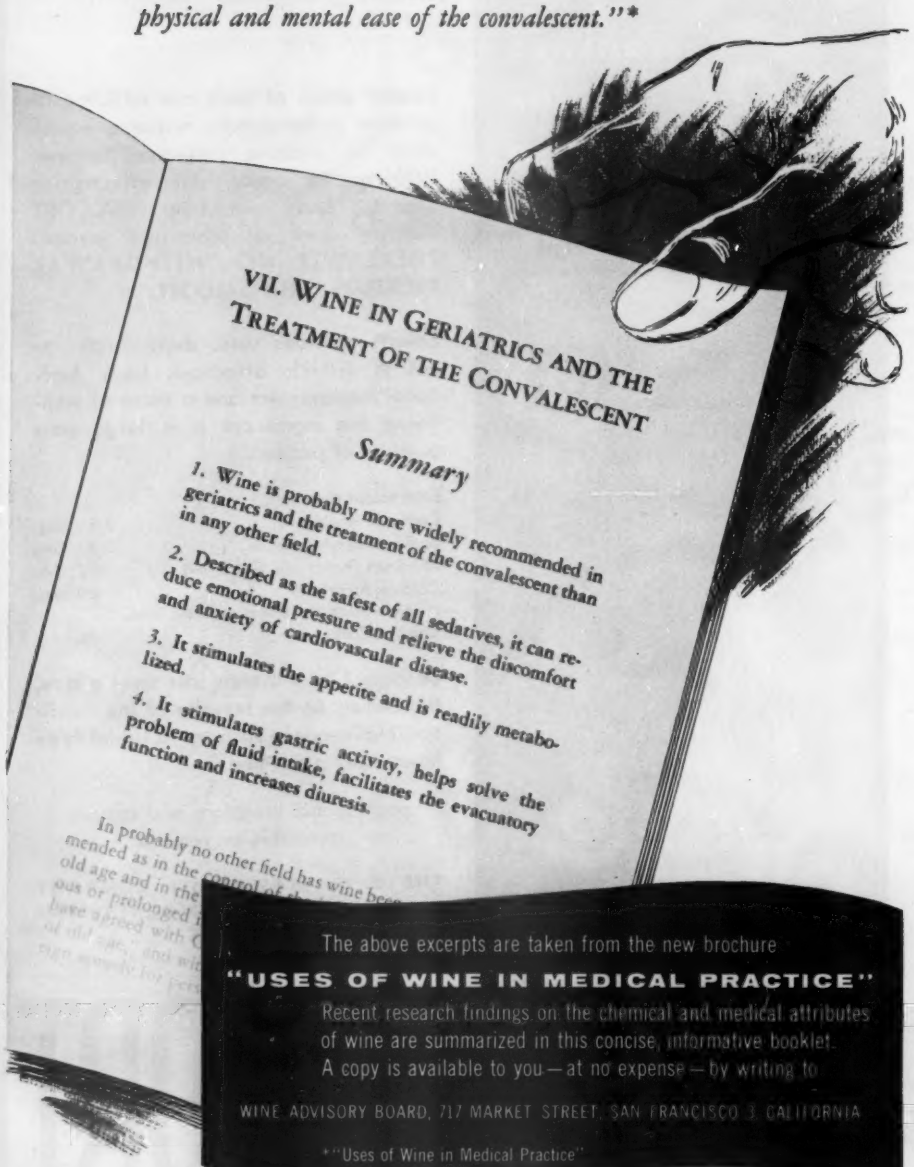
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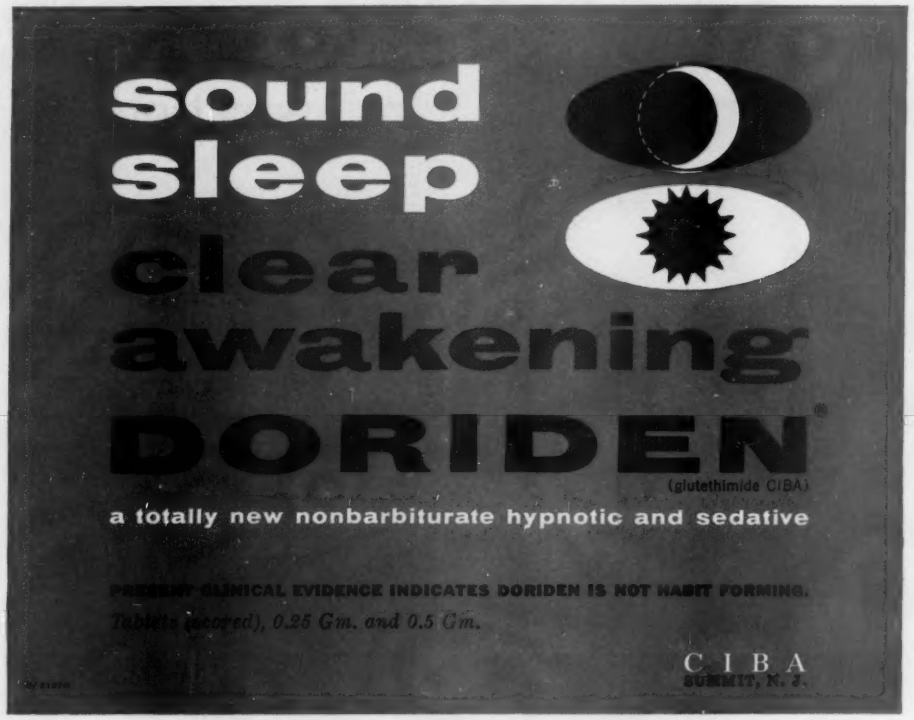

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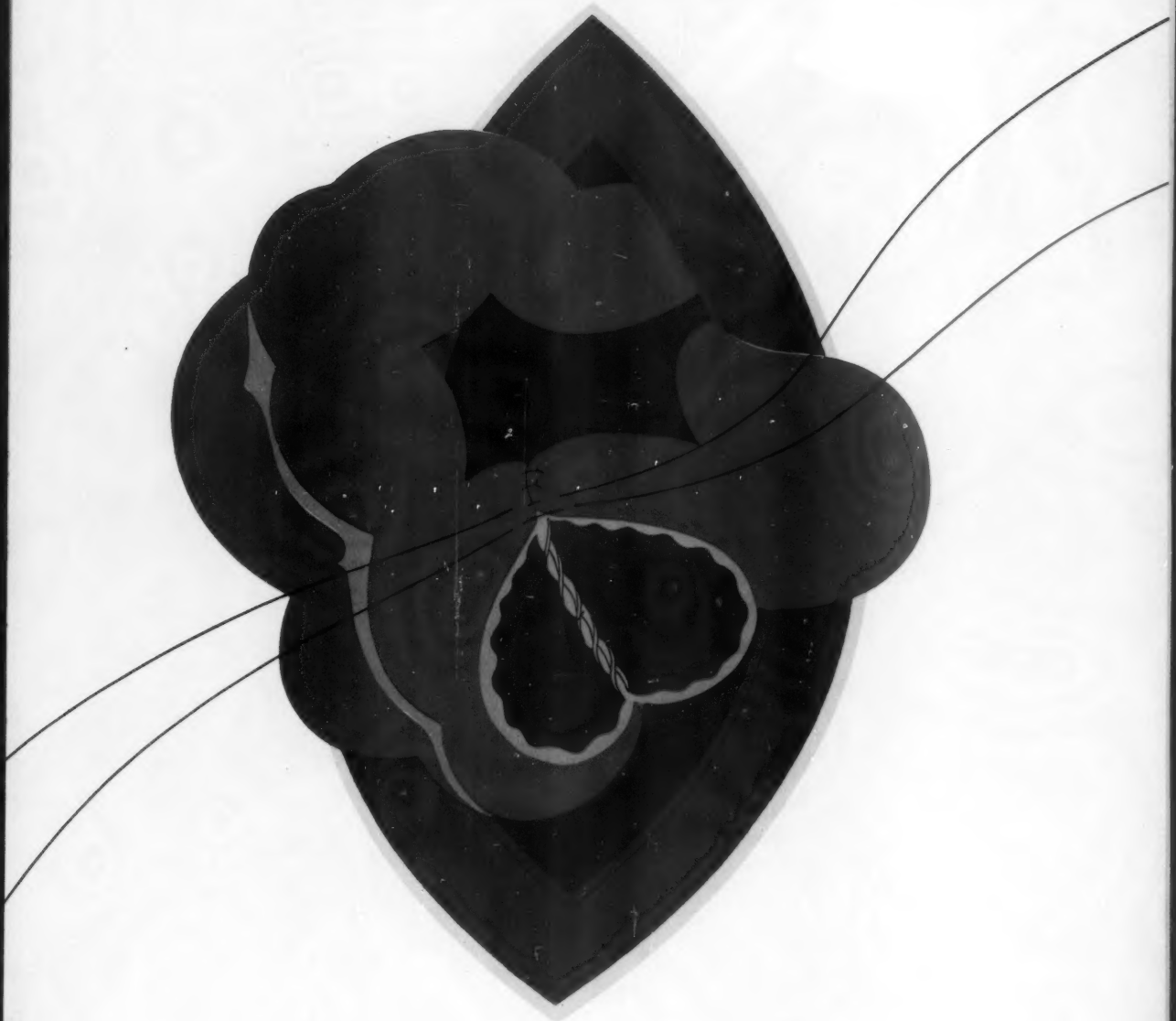

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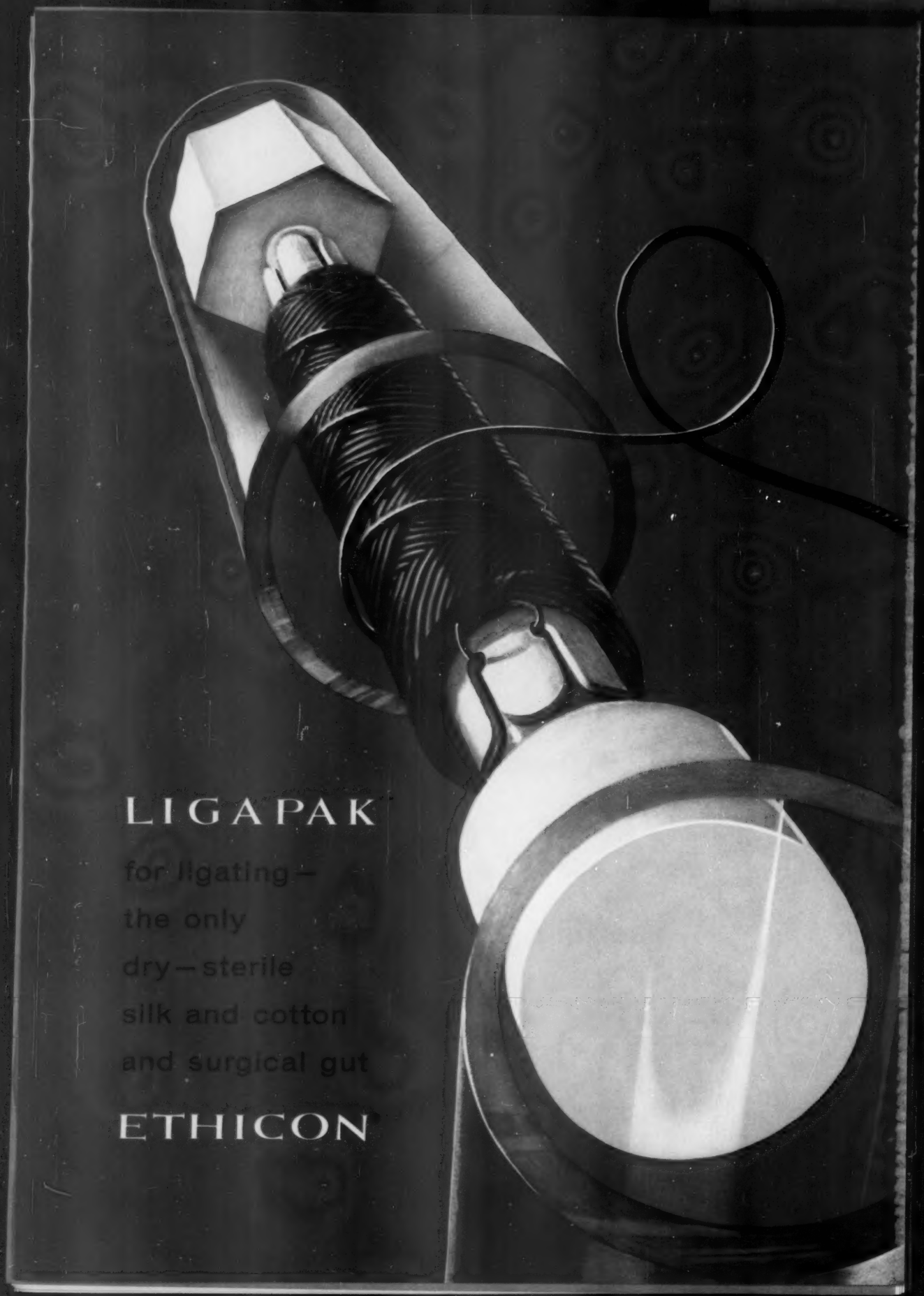
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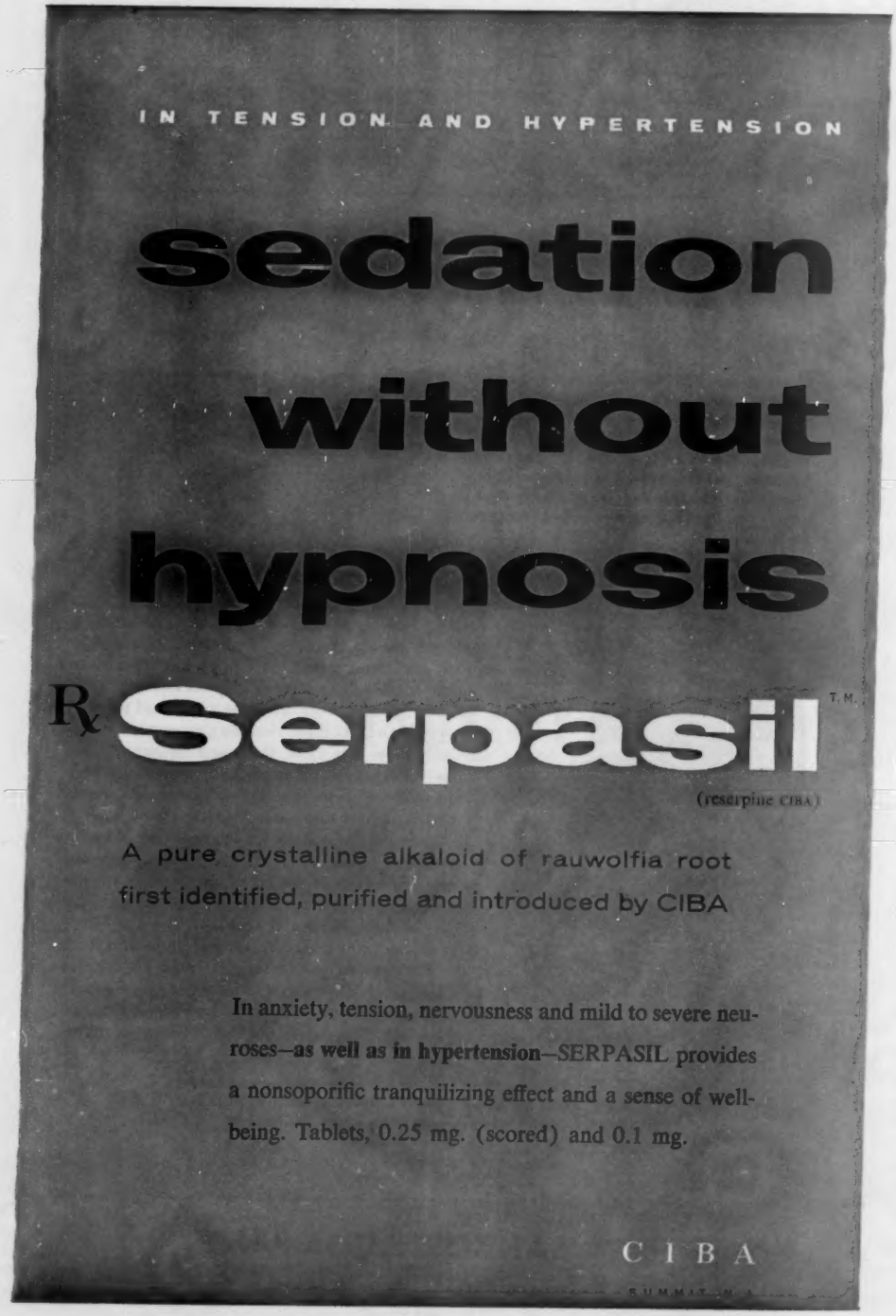
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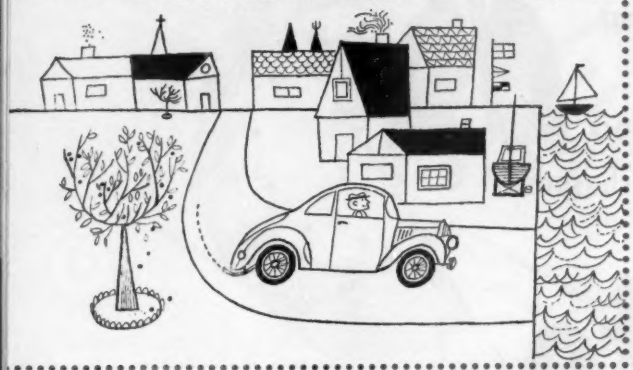

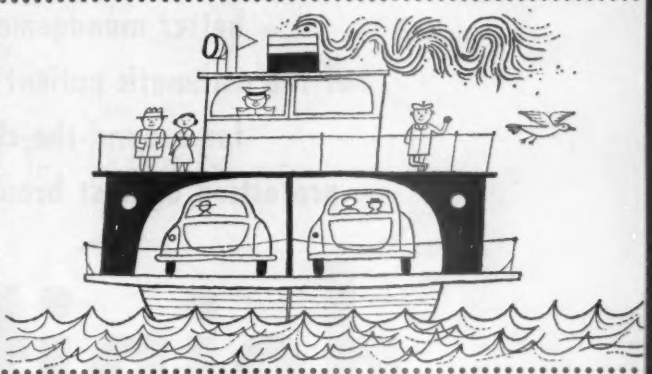

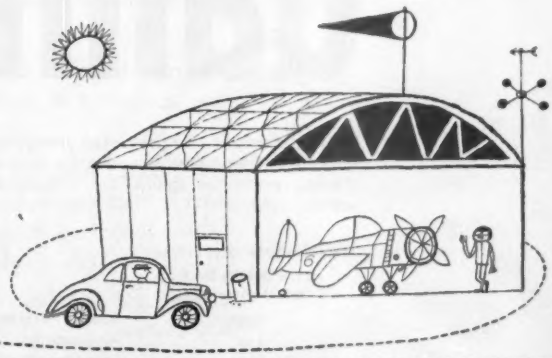

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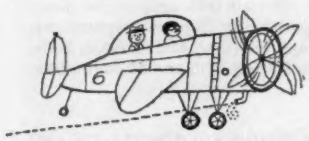

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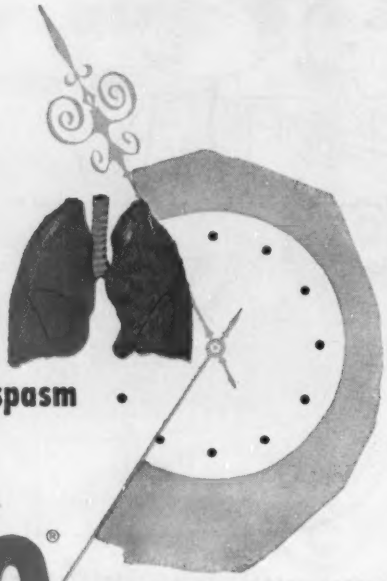

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[*Wallis, R.: New York State J. Med. 55:243 (Jan. 15) 1955.*]

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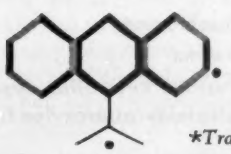

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CANCER OF THE LARYNX*

Five-Year Results, with Emphasis on Radiotherapy

C. C. WANG, M.D.,† AND A. R. O'DONNELL, M.D.‡

BOSTON

SINCE Coutard[1] described a group of patients with inoperable cancer of the larynx successfully treated by radiation in the early 1930's, radiotherapy as well as surgery has been accepted as a useful means of dealing with this disease. Numerous valuable contributions have subsequently appeared in the literature. The present report deals mainly with the evaluation of therapeutic results in a group of 253 patients in whom the cancer arose on the vocal cords or had extended to involve the immediately adjacent structures — that is, endolaryngeal tumors. All cases were histologically proved. The group included patients who were registered in the Tumor Clinic or were seen in the Department of Radiology at the Massachusetts General Hospital from 1931 to 1949 inclusive. This interval allows for a minimum follow-up period of five years on all patients. Private patients treated only by surgery at the Massachusetts Eye and Ear Infirmary and not registered in the Tumor Clinic were not included.

DIAGNOSIS

It cannot be overemphasized that accurate determination and description of the location and extent of the tumor in the larynx is essential to the proper management of the disease and estimation of its probable outcome. Indirect laryngoscopic examination to observe the motion of the vocal cords and the adjacent structures is important, but direct laryngoscopy should follow for accurate assessment of the extent of the lesion and to obtain a tissue biopsy to confirm the diagnosis. Frequently, the subglottic extension cannot be well visualized by direct or indirect laryngoscopy, but may be more completely demonstrated by radiography. Therefore, soft-tissue technic, with lateral views, and laminagraphy in anteroposterior projection of the neck are often useful for the visualization of the vocal cords and their adjacent structures (Fig. 1). Only by these measures can the extent of the tumor sometimes be determined, or the presence of cartilaginous involvement shown. Clinically, careful palpation of the neck must be done to ascertain the presence or absence of metastatic disease in the lymph nodes.

GENERAL CLINICAL DATA

As shown in Figure 2 approximately two thirds of the patients were in the sixth and seventh decades; less than 5 per cent were under the age of forty. It is strikingly evident that cancer of the larynx is a disease of men: 240, or 95 per cent, of the entire group were males, or a ratio of 19 men to 1 woman.

Histologically, only 1 case of the total 253 was adenocarcinoma; the remainder were squamous-cell carcinoma. Primary radiation treatment was given to 161, and surgery to 84 patients; 8 received no treatment.

CLASSIFICATION OF DISEASE

In evaluating the results of any form of treatment of neoplastic disease, it is essential to classify the stage of the disease. It is evident that whatever success may be expected from any form of treatment of a very early lesion cannot also be anticipated in the treatment of advanced tumors. In this study, therefore, two major points were covered; an acceptable, recognized classification of laryngeal cancer was arbitrarily chosen, and all patients, so far as possible, classified accordingly; and the evaluation of the results was based on the stage of disease at the time of therapy. A brief summary of the classification of Nielsen and Strandberg[2] follows:

Stage 1. The tumor is limited to the anterior two thirds of one of the true vocal cords (Fig. 3). The mobility of the cord is unimpaired. Perhaps there is invasion of the anterior commissure, but no farther extension.

*From the Department of Radiology, Massachusetts General Hospital.
†Teaching fellow in radiology, Harvard Medical School; clinical fellow, Department of Radiology, Massachusetts General Hospital.
‡Clinical assistant in radiology, Massachusetts General Hospital.

Stage 2. The tumor involves the anterior commissure and (perhaps) a greater or lesser part of the anterior two thirds of the true vocal cord (Fig. 4). The mobility of the cord is unimpaired.

FIGURE 1. *Laminagraph of the Larynx in the Anteroposterior Projection, Showing a Tumor Involving the Right False and True Vocal Cords Filling the Laryngeal Ventricle, with Subglottic Extension.*

Stage 3. The tumor extends beyond the vocal cord, which is more or less fixed (Fig. 5). Involvement is unilateral or bilateral. No lymph nodes are affected.

Stage 4. Extension of the tumor beyond the larynx, frequently with lymph-node involvement (Fig. 6).

Table 1 shows the types of treatment according to the stage of the disease. Of the entire group of 253 patients 50 exhibited Stage 1 and 31 Stage 2 cancers; as would have been expected there were many more in Stage 3, 105 cases, and in Stage 4, 53. Six patients could not be classified because of insufficient clinical data; 8 received no treatment.

RESULTS OF TREATMENT

The results of treatment in relation to the various stages of disease are presented in Tables 2 to 5. In this analysis a patient in whom radiotherapy as a primary treatment failed and who was subsequently cured by surgery, or vice versa, is considered a failure of the first method employed.

Thirty-five patients with Stage 1 disease were treated by radiotherapy as the primary method (Table 2). At the end of five years, 28 patients, or 80 per cent, were known to have survived symptom free; of 15 patients treated by surgery 13, or 86.6 per cent, were alive and symptom free.

Of 19 patients with Stage 2 disease treated by radiotherapy 13, or 68.4 per cent, were alive and well at the end of five years (Table 3). Of 12 patients treated by surgery 7, or 58.3 per cent, survived.

The operations performed in the cases of early cancer were as follows: 15 patients had total laryngectomy, 5 in Stage 1 and 10 in Stage 2 of the disease; 12 had laryngofissure with excision of the tumor, 10 in Stage 1 and 2 in Stage 2.

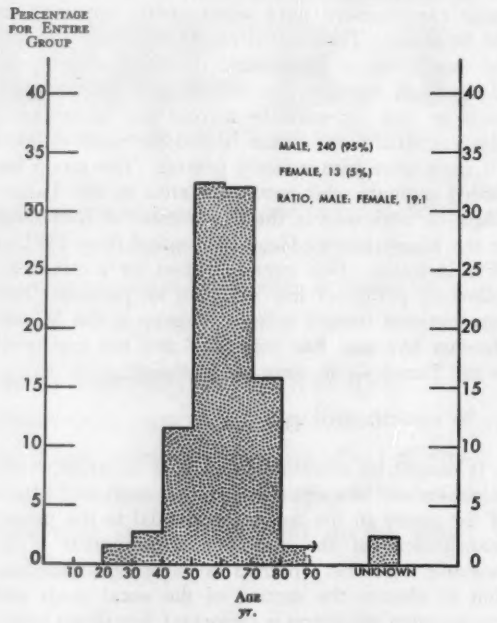

FIGURE 2. *Age and Sex Frequency.*

Of the patients with Stage 3 disease (Table 4) 58 were treated by radiotherapy, with 14, or 24 per cent, five-year survivals; of 47 surgically treated 25, or 53 per cent, survived for five years. Because of insufficient clinical data it was impossible to classify the cases in the Stage 3 group according to the location and extent of the lesions. It should be noted, however, that these patients with subglottic extension appeared to do better with surgery than radio-

therapy; those with involvement of the ventricular band showed less advantage from surgery than the former group.

FIGURE 3. *Cancer of the Larynx, Stage 1.*

In Table 5 cases in Stage 4 are divided into two subgroups. Of the 18 cases considered Stage 4 by virtue of direct extension from the larynx to the

FIGURE 4. *Cancer of the Larynx, Stage 2.*

hypopharyngeal structures but without clinical metastatic involvement of lymph nodes 14 were irradiated, with 4 (28.6 per cent) five-year survivals. The remaining 4 were treated surgically, and only 1 (25 per cent) survived for five years symptom free. Thirty-five patients were regarded as Stage 4 because of the presence of cervical-lymph-node metastases. Of these, 32 were treated by radiotherapy, only 3 (9.4 per cent) surviving for five years; of the 3 subjected to radical surgery none survived that long.

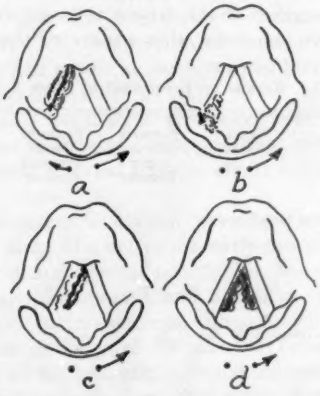

FIGURE 5. *Cancer of the Larynx, Stage 3.*
a=*invasion of the vocal muscle, perhaps of the sinus of Morgagni and the false vocal cord (perhaps of the subglottis).*
b=*extension to the anterior side of the arytenoid region.*
c=*extension to the subglottis.*
d=*tumor arising in the subglottis.*

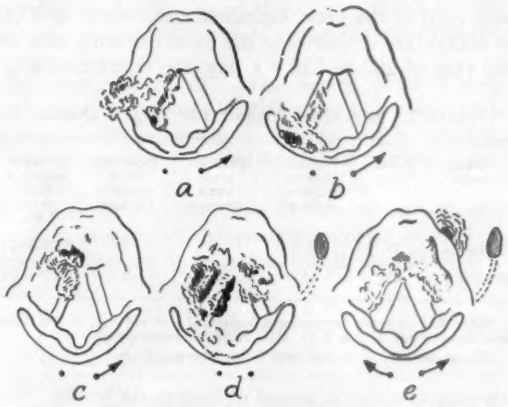

FIGURE 6. *Cancer of the Larynx, Stage 4.*
a=*invasion of the pharyngoepiglottic fold.*
b=*infiltration of the arytenoid region.*
c=*infiltration of the epiglottis.*
d=*diffuse tumor growth in the interior of the larynx, with destruction of the cartilage (as a rule lymph nodes are involved).*
e=*tumor arising from the false vocal cord, or from the laryngeal surface of the epiglottis, frequently with extension to the pre-epiglottic space (as a rule lymph nodes are involved).*

Of the 6 patients in whom classification of disease was impossible, 3 were given radiation therapy, and none survived for five years; 3 were given surgical care, 1 of whom was living twenty years after a total laryngectomy.

RADIATION TECHNIC

In radiation therapy of cancer of the larynx the first treatment must be the correct one, for there is seldom a second opportunity for cure. The therapeutic procedure should therefore be carefully planned and carried out. Well filtered 200-K.V. x-ray with at least 0.5-mm. copper filter (half-value layer of 1 mm. of copper) has been used with satisfactory results at the Massachusetts General Hospital for the

TABLE 1. *Classification of Treated Cases.*

STAGE OF DISEASE	PATIENTS TREATED BY RADIATION	PATIENTS TREATED BY SURGERY	TOTALS
1	35	15	50
2	19	12	31
3	58	47	105
4	46	7	53
Unclassified	3	3	6
Totals	161	84	245

past two decades. Two direct opposing portals with a field size of 4 by 5 cm. for the vocal-cord lesions and 6 by 8 cm. for more extensive disease are employed. Daily treatments are given alternately to both sides of the neck. Estimated tissue doses of 5000 to 6000 r are delivered to the cancer-bearing area at the rate of 200 to 250 r a day, the entire course of therapy covering a period of four to six weeks. This amount of radiation should produce a skin reaction in the form of a brisk, wet radiodermatitis, particularly at the anterior midline of the neck, since the two lateral portals of entry must be overlapped at this point. During the course of treatments regular, frequent indirect laryngoscopic examinations are mandatory to follow the response of the tumor and disclose possible laryngeal edema. The edema should be avoided, for it may narrow the glottic space and decrease the radioresponsiveness of the tumor. Accurate direction of the x-ray beam is vital since the treatment field is small, and routine setting up of the patient is therefore of even greater importance than usual. This should be done by the radiologist himself rather than by the technician, and should be checked with radiography to ascertain that the tumor tissue is well within the beam.

Since the advent of supervoltage x-rays — for example 1000 to 3000 K.V. — it is possible to deliver a cancerocidal dose to the entire tumor of the larynx through a single lateral portal. A moderate skin reaction in the form of dry radiodermatitis usually results. In cases of subglottic or more extensive lesions that require a larger x-ray dose infinite portals of entry in the form of rotation technic can be employed with resultant minimal skin reaction. It should be noted that aside from the skin-sparing effect and the better defined and more penetrating beam, no more significant benefit, as far as cure of this disease is concerned, is obtained with supervoltage than with the conventional 200-K.V. x-ray unit.

TABLE 2. *Results of Treatment of Stage 1 Disease.*

Treatment	Total Cases	Patient Lost to Follow-up Study	Patients Dead with Disease	Patients Dead without Disease	Patients Symptom Free after 5 Yr.
Radiation	35	0	4	3*	28(80.0%)
Surgery	15	1†	1	0	13(86.6%)

*One died of acute myelogenous leukemia, 1 of old age, & 1 of cerebral hemorrhage 1, 2 & 3 yr. after radiation respectively.
†No recurrence when last seen 2 yr. postoperatively.

TABLE 3. *Results of Treatment of Stage 2 Disease.*

Treatment	Total Cases	Patients Lost to Follow-up Study	Patients Dead with Disease	Patients Dead without Disease	Patients Symptom Free after 5 Yr.
Radiation	19	2*	3	1†	13(68.4%)
Surgery	12	0	4	1‡	7(58.3%)

*Lost 30 and 48 mo. after treatment.
†Died without recurrence 11 mo. after radiation.
‡Died without disease 4 yr. after surgery.

Discussion

The present study confirms the growing recognition that early cancer of the larynx is one of the "curable cancers" treated either by surgery or radiotherapy. As far as cure is concerned there is no significant difference between these two methods in the early stages of the disease. However, the advantage of radiation therapy (a great one that should make it the treatment of choice in this group) is the preservation of a useful voice in addition to the eradication of the cancer.

In the later stages the situation is quite different. The cures by surgery surpass those of radiotherapy, and the sacrifice of the larynx is probably justified. It is known, however, that cancer of the larynx is peculiar in that the site of origin has a vast bearing on its development, growth and prognosis. In cancer that is Stage 3 because of involvement of the ventricular band the relative advantage of surgery over radiotherapy is smaller. In fact such patients seem to respond well to radiation and may show a high rate of curability. Since in 25 per cent of the

TABLE 4. *Results of Treatment of Stage 3 Disease.*

Treatment	Total Cases	Patients Dead with Disease	Patients Dead without Disease	Patients Symptom Free after 5 Yr.
Radiation	58	40	4*	14(24.0%)
Surgery	47	19	3†	25(53.0%)

*Died without recurrence 20 & 28 mo. & 3½ & 4½ yr. respectively after treatment.
†Died without laryngeal disease 10 mo. (of cancer of lung), 4 yr. & 4¼ yr. (suicide) postoperatively.

TABLE 5. *Results of Treatment of Stage 4 Disease.*

Treatment	Total Cases	Patients Dead with Disease	Patients Dead without Disease	Patients Symptom Free after 5 Yr.
Patients without lymph-node involvement:				
Radiation	14	9	1*	4(28.6%)
Surgery	4	3	0	1(25.0%)
Patients with lymph-node involvement:				
Radiation	32	27	2†	3(9.4%)
Surgery	3	3	0	0

*Died 4 yr. & 9 mo. after irradiation.
†One died 20 mo. after irradiation; other, at autopsy 1 mo. after treatment, showed no cancer.

entire group with Stage 3 disease cancer may be controlled by radiotherapy with preservation of voice, a fair trial of this conservative method should be carried out, especially for patients with supraglottic extension. This is true provided the patient can be closely followed and the tumor carefully observed. If the tumor does not respond favorably to radiation total laryngectomy may still be done.

In Stage 4, when remote metastases have developed, the results by radiotherapy and surgery are equally poor. Even in this group, however, if no cervical lymph nodes are involved, 1 in 4 patients may survive symptom free for five years after radiotherapy.

Summary and Conclusions

Two hundred and fifty-three cases of proved cancer of the larynx, seen in the Tumor Clinic and the Department of Radiology at the Massachusetts General Hospital from 1931 to 1949 inclusive, are classified according to the stage of the disease, and the therapeutic five-year results are evaluated.

The treatment of early cancer of the vocal cords, Stage 1 and 2, by either radiotherapy or surgery is attended by a high degree of success. The preservation of a useful voice should make radiotherapy the treatment of choice.

In advanced cancer of the larynx, Stage 3 with supraglottic extension, a trial of radiotherapy may be carried out when careful observation is possible. If the disease is not controlled radical surgery is still available.

It is evident that the closest co-operation between the radiologist and the otolaryngologist is vital if maximum benefit is to follow the treatment of this disease.

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GALACTOSEMIA WITH CATARACTS*

Report of a Case, with Notes on Physiopathology

Joseph A. Ritter, M.D.,† and Edward J. Cannon, M.D.‡

PHILADELPHIA

GALACTOSEMIA, an inborn error in the metabolism of ingested galactose, is today a well established clinical entity. The earliest reports were those of Reuss[1] in 1908, Göppert[2] in 1917 and Fanconi[3] in 1933. The first report in the American literature was by Mason and Turner[4] in 1935. Over the past ten years probably less than 30 cases have been recorded, but it seems reasonable to suppose that many others have not been reported and still others have gone unrecognized.

The characteristic clinical manifestations of this congenital metabolic defect are early nutritional failure, physical and mental retardation, hepatomegaly, splenomegaly, osteoporosis and cataracts. Melituria, albuminuria, amino-aciduria, impairment in liver function and elevation of the galactose content of the blood may all be detected. Affected infants often appear normal at birth, but after a few days of milk feeding, vomiting, lethargy, failure to gain weight and enlargement of the liver become apparent. Ascites and edema may develop. In some infants the duration of physiologic jaundice is unduly prolonged. Mild cases may go unrecognized until cataracts and nutritional failure develop or melituria is detected. In severe cases the disease is often fulminating, and death may occur in the neonatal period or soon thereafter. Infants who survive are usually malnourished and dwarfed at two or three months of age, and cataracts and mental retardation may be discerned. Those who succumb at an early age commonly show jaundice, fatty degeneration of the liver and a hemorrhagic diathesis.[5] A striking feature of the disease is the regression and reversibility of signs and symptoms after deletion of milk and milk products from the diet.

The present case of galactosemia is being reported because the patient is six and one-half years old and is thus the second oldest child recorded in the literature. The oldest patient whose history has been recorded was nine years old,[5] and the diagnosis in this case has been questioned.[6] The third oldest patient was six years of age, when the report appeared in 1935.[4]

Case Report

G.B. was born spontaneously of a 28-year-old toxemic mother on May 8, 1947. Her birth weight was 1.4 kg. (3 pounds, 14 ounces), and she was confined to an incubator for the 1st month of life. She was fed powdered milk, the composition of which could not be ascertained, from birth to 1 year of age. The parents considered her physical and mental development normal except for poor vision, a defect that had become more apparent since the age of 4 years.

She was admitted to the Reese Clinic of the Wills Eye Hospital on August 21, 1951, at the age of 4 3/12 years, for treatment of bilateral cataracts. Physical examination by

*Presented in part before the Section of Ophthalmology of the College of Physicians of Philadelphia on February 19, 1953.

From the Pediatric Department, Graduate Hospital, Graduate School of Medicine, University of Pennsylvania, and Wills Eye Hospital.

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‡Clinical assistant, Wills Eye Hospital.

an ophthalmologic resident was reported as negative except for the eyes. Vision was restricted to "light perception" in both eyes, and with dilated pupils she could "count only fingers" at 1 meter. The periphery of the ocular fundi could be seen and was considered normal in the visible portion. Zonular cataracts were found involving the fetal and infantile nucleus, with a few opacities at the embryonal nucleus. Biomicroscopy likewise revealed typical zonular cataracts. A single urinalysis on August 22 disclosed melituria, but no follow-up studies were done. A discission was performed on the right eye on August 24. Postoperatively there was good

FIGURE 1. *Appearance of the Patient on March 17, 1952.*

"fluffing" of the cortex of the lens, and she was discharged on September 1.

The 2d admission was on February 27, 1952, at the age of 4 9/12 years. Examination revealed a frail, apprehensive, sallow child, with slender fingers, brachycephalic head and prominent bosses. A tracheotomy scar was evident, the result of a respiratory infection at 7 months of age. There was slight enlargement of the axillary and inguinal lymph nodes. Caries was moderately advanced. Examination of the heart and lungs revealed no abnormal findings. The liver extended 4 cm. below the right costal margin. Urinalysis on February 27 was positive for sugar (2 per cent) and acetone (++++), but no diacetic acid was present. Subsequent specimens showed 2 per cent or more of a reducing substance, and all were positive for albumin. Examination of the blood on February 29 demonstrated a red-cell count of 4,130,000, with a hemoglobin of 13 gm. per 100 cc., and a white-cell count of 13,650, with 63 per cent neutrophils, 33 per cent lymphocytes, 2 per cent monocytes and 2 per cent eosinophils. The sedimentation rate was 1 mm. in 60 minutes. The fasting blood sugar was 78 mg. per 100 cc., and the carbon dioxide content of the blood 48 vol. per cent. Blood Wassermann and Kahn tests for syphilis were negative. Roentgenograms of the skull, hands, feet, legs and pelvis were normal.

A discission was again performed on the right eye. There was good "fluffing," and the postoperative course was without incident. The patient's appearance is shown in Figure 1, with a close-up of the eyes in Figure 2.

Further studies after operation disclosed that the urinary reducing substance was nonfermentable, and paper chromatography of the urine,* indicated that galactose was present in the urine in a concentration of approximately 535 mg. per 100 cc.

The patient was transferred to the Pediatric Department of the Graduate Hospital on March 18. She weighed 14.1 kg. (31 pounds), and physical examination was unchanged. Laboratory studies showed the 1-minute direct-reacting bilirubin to measure 0.37 mg., and the total 0.59 mg. per 100 cc. of blood. The fasting total blood sugar level was 225 mg., and the blood urea nitrogen 15 mg. per 100 cc. She was given a milk-free diet, and on March 26 the fasting total blood sugar content was 96 mg. per 100 cc. The prothrombin time was 17 seconds, or 75 per cent. Melituria had disappeared. An electrocardiogram was considered normal.

At discharge on March 26 the weight was 14.5 kg. (32 pounds). On re-examination on May 6 the weight was 15.9 kg. (35 pounds), and the height 102 cm. (40 inches). The liver was not palpable. Examination on August 12 revealed a good opening in the capsule of the right eye, with a major portion of the cortex already absorbed. There was no evident change in the left eye, which still showed a zonular cataract.

The patient was readmitted to the Wills Eye Hospital on November 5 at the age of 5 6/12 years. The right eye demonstrated a large central capsular opening (Fig. 3), but ophthalmoscopic examination on the right was otherwise negative. A red fundus reflex was obtained from the left eye; the zonular cataract was unchanged after 8 months of a galactose-free diet. A routine urinalysis on November 7 was normal. Chromatographic studies were repeated†; the specimens obtained were developed with butanol and 5 per cent ammonia. The urine obtained on November 6 showed a spot corresponding to galactose, but none was present in the urine on November 11. Both these specimens and filtrates of blood drawn on the same dates indicated a large spot below the origin, giving a color with meta-phenylene diamine before heating. This probably represented ascorbic acid, but the identity was not verified by isolation.

FIGURE 2. *"Fluffing" after the Second Discission of the Right Eye.*

After a discission of the left eye on November 7 and a linear extraction 7 days later the patient was finally discharged on November 21. Figure 4 demonstrates her appearance on November 20, 1953.

DISCUSSION

Lactose, the carbohydrate of mammalian milk, is composed of galactose and glucose in beta linkage. In the small intestine lactose is hydrolyzed into galactose and glucose by the enzymatic action of lactase. The metabolism of galactose is more complicated than that of glucose, and the mechanisms involved are not entirely clear. Under normal conditions galactose is converted in the liver to galactose-l-phosphate by means of adenosine triphosphate, in the presence

*Performed by D. B. McN. Scott, Ph.D., at the Children's Hospital of Philadelphia, with the technic of Partridge and Westall.[7]

†By Dr. D. B. McN. Scott.

of an enzyme galactokinase. The galactose-l-phosphate formed is transformed into glucose-l-phosphate, which is then converted into glucose-6-phosphate, a product that is subsequently metabolized in accordance with the classic glycolytic scheme to produce pyruvic or lactic acid.

The present knowledge of the metabolic behavior of galactose may be summarized by three equations,[8-15] as follows:

Galactose + adenosine triphosphate $\xrightarrow{\text{(galactokinase)}}$ galactose-l-phosphate + adenosine diphosphate.

Galactose-l-phosphate $\xrightarrow[\text{(uridine-diphosphate-glucose)}]{\text{(phosphogalactoisomerase)}}$ glucose-l-phosphate + uridine-diphosphate-galactose.

Glucose-l-phosphate $\underset{\text{(glucose-l, 6-diphosphate)}}{\overset{\text{(phosphoglucomutase)}}{\rightleftharpoons}}$ glucose-6-phosphate.

The first reaction is quite analogous to the first step in the glycolysis of glucose and fructose to give G-6-PO_4 and F-6-PO_4 or F-l-PO_4. This reaction is mediated by an enzyme referred to as galactokinase, although it is not known whether this is the same as or different from the fructokinase or glucokinase — that is, the enzyme responsible for the phosphorylation of fructose and glucose. That Ga-l-PO_4 is formed from galactose in vivo was demonstrated in rats and rabbits fed large quantities of galactose. Under these conditions Ga-l-PO_4 was shown to accumulate in the liver.[9,11,12]

FIGURE 3. *Appearance of the Eyes on November 6, 1952, Showing a Central Capsular Opening of the Right and a Zonular Cataract of the Left Eye.*

The second reaction is a distinctively novel type of enzymatic reaction involving a Walden inversion of carbon atom-4 resulting in the formation of glucose.[10,13,15] This is formulated as occurring in two steps:

UDPG + Galactose-l-PO_4 $\rightleftharpoons$ UDPGa + Glucose-l-PO_4

UDPGalactose $\rightleftharpoons$ UDPGlucose

The first step represents an exchange of G-l-PO_4 for Ga-l-PO_4 by the coenzyme, uridine-diphosphate-glucose. The resulting UDPGa enters into an equilibrium with UDPG in a ratio 1:3. The enzyme, phosphogalactoisomerase, is said to mediate this equilibrium and serves to facilitate the regeneration of UDPG, which can again participate in the first step. The mechanisms of these two steps are still unknown.

FIGURE 4. *Appearance of the Patient on November 20, 1953, When She Was Aphakic but of Normal Physical and Mental Development.*

The third reaction is a very common one, occurring in practically every animal tissue investigated, and is mediated by the enzyme phosphoglucomutase. The coenzyme involved in this reaction is glucose-l, 6-diphosphate.[9,14] These biochemical reactions have been elucidated from a study of yeasts and rat and rabbit livers as well as other tissues.

The available knowledge regarding galactosemia is limited, and the normal metabolism of galactose is not yet entirely known. Recent studies[16] have indicated that in nearly normal, nongalactosemic infants, under a variety of circumstances, the galactose content of the blood may reach 40 per cent of the total blood sugar. Normal infants not receiving foods containing lactose or galactose had no demonstrable galactose in the blood. In 1 galactosemic infant, not receiving such food, small amounts of galactose were determined in the blood, suggesting that galactose was formed from glucose. The same authors warn that unless galactose and glucose are separately determined in infants with a specific defect in the metabolism of galactose, hypoglycemia may escape detection.

The normal liver is chiefly concerned, but not entirely, in the conversion of galactose to glucose for immediate utilization or storage in the form of glycogen for later utilization.[17] That the liver has a limited capacity to metabolize galactose is attested by the galactose tolerance test for measuring this function in suspected cases of hepatocellular damage. There is no renal threshold for galactose. In galactosemia, secondary amino-aciduria has been detected by partition chromatography. This may be due to competitive reabsorption at the level of the renal tubule, or the amino-aciduria may be specific for galactosemia with a specific renal mechanism.[18] In galactosemia the ability of the liver to metabolize galactose is apparently not entirely lost, and some is probably stored.[2,4,6,19] Glycogen, irrespective of its derivation, gives up only glucose; galactose in the circulating blood comes only from ingested galactose, and the recent reported exception in a galactosemic infant needs further substantiation.[16] The defect in galactosemia is probably congenital, and a genetic association has been demonstrated.[2,5,20,21] The nature of the specific defect in galactosemia is probably in the Waldenase system or in some hormonal aberrations that derange it.

Available data suggest that galactose per se is cytotoxic, and this would explain in a great measure the symptoms and signs of this disorder. Depression of the glucose level of the blood is not a constant finding,[6] but when present may produce irreversible hypoglycemia.[21] Bruck and Rapoport[6] believe that glucose and galactose compete in a common metabolic mechanism, probably in the liver. They do not believe that the low blood glucose level per se causes any of the symptoms in galactosemic patients because of the dissimilarity of symptoms to those noted in glycogen-storage disease and in hyperinsulinism. Glycogenolysis occurs normally in galactosemia, and glucose tolerance tests are reported as being normal.[6,19,20] The reciprocal interrelation between galactose and glucose[4,6,16,19,20,22] suggests an applicability in the treatment of galactosemia.[19] Galactose tolerance tests in persons without a specific defect in galactose metabolism show a similar reciprocal relation.[16,23] Long follow-up studies of galactosemic patients, in 1 case to the age of eighteen, have shown that the intolerance to galactose does not disappear although it may diminish.[2,20,21,24]

Studies made of the liver in a limited number of cases have failed to reveal specific changes. Typical Laënnec cirrhosis has been found at autopsy[1,21,25] and by needle biopsy in a one-year-old infant.[21] Adenomas laden with glycogen and associated with cirrhosis[26] have also been noted. Fatty infiltration of the liver has been the outstanding pathological finding.[5,27] Early hepatic changes in galactosemia are reversible; when galactose ingestion is stopped, liver function improves, and the size of the liver decreases. Another evidence of reversibility of the hepatic damage commonly present in this disorder is the regression of jaundice in infants placed on a galactose-restricted diet.

Cataracts have been noted in approximately half the reported cases of galactosemia. The youngest patients in whom this association was diagnosed were between six and seven and a half weeks old, and the oldest was nine years old.[2,5,6,28,29] The cataracts in galactosemic patients have been described mainly as zonular or lamellar and in a few cases as anterior cortical or nuclear. The most frequently observed opacity is a central refractile ring that resembles the "oil drop" effect of lenticonus; new opacities perhaps indicate a failure to maintain a galactose-free diet.[30] With few exceptions galactosemic cataracts resorbed or showed various degrees of regression when milk and milk products were deleted from the diet, particularly if the disease was diagnosed and treatment started before the patient was three months of age.

Experimental evidence has been advanced that galactose is directly toxic to the lenticular epithelium.[31-35] The lenses of young animals appear to be more vulnerable than those of older ones. The degree of reversibility of these experimentally induced cataracts depended in part on the extent of nuclear and cortical opacifications at the time galactose was removed from the ration. The severity and progression of the cataracts showed a direct relation to the level and duration of the galactosemia.

Certain histologic and biochemical changes have been noted in experimental galactose-induced cataracts in rats. The earliest histologic change was liquefaction of the cortical fibers near the equator of the lens. Later changes occurred in the capsular epithelium and nuclear area. Resorbed cataracts ophthalmologically appeared normal but microscopically showed degenerated fibers adjacent to the nucleus.[36] The biochemical aberrations were varied. A decrease in the sulfhydryl and vitamin C content of the lens precedes any cataractous alterations.[37] Cystine and cortical glutathione is appreciably diminished, and in mature cataracts nuclear glutathione is also lost.[38] The total ash content is increased,[39] and the electric potential is elevated in the central portion of the lens of young rats.[40] Galactose produces altered osmotic relations between the lens and the surrounding media.[41,42] In experiments with lens extracts at the Wills Eye Hospital Research Laboratory[43] and in Germany,[44] it was found that the lens can metabolize galactose but at a considerably slower rate than glucose.

To understand fully cataractogenesis due to galactosemia it would be necessary to understand the metabolic behavior of the normal lens. The major source of energy in the lens is glucose, although the metabolic pathway that glucose travels in the lens to lactic acid is still not completely known. It has been found that with bovine eyes, as the age of the lens increases, the rate of glucose disappearance is diminished. With the inception of cataract formation this rate is further

decreased until in a mature cataract hardly any carbohydrate metabolism is measurable. In the present state of knowledge of lenticular metabolism, the assumption may be made that diminution in the normal metabolic rate of glucose utilization by the lens, however produced, may predispose to the development of cataract. In examining the known biochemistry of galactose one is presented with several ways in which excess galactose may interfere with normal glucose metabolism in the lens, assuming of course, that the reactions discussed previously occur in this tissue. If it is assumed that the hexokinase in the first reaction is the same enzyme that mediates the phosphorylation of glucose in the lens, competition exists between the affinity of galactose and glucose for this same enzyme. With increasing concentration of galactose, as in galactosemia, the availability of the enzyme for glucose may be strongly limited. In the Wills Eye Hospital Research Laboratory[43] it has been found that the decrease in the rate of glucose metabolism with increasing size of the rabbit lens may be directly related to the concentration of hexokinase, which is a very sensitive enzyme. That galactose itself inhibits the enzyme is another possibility. As mentioned above, in the presence of excessive amounts of galactose, galactose-l-PO_4 accumulates. This accumulation of galactose-l-PO_4 may interfere with the normal rate of conversion to glucose-l-PO_4 (second equation listed above), by impeding the first step or second step in the Walden inversion or both. In this connection it is also conceivable that large amounts of galactose-l-PO_4 interfere with the synthesis of the coenzyme, UDPG, which is an absolute requirement for the reaction.

The accumulation of galactose-l-PO_4 may interfere in another way—namely, in the third reaction. Even if galactose-l-PO_4 is converted to galactose-6-PO_4, the latter is probably not metabolically active. Apparently, the lens can metabolize small amounts of galactose under normal conditions. In galactosemia, however, the normal carbohydrate metabolism of the lens may be directly disrupted. Since the lens depends on the glycolysis of glucose for its source of energy with which to carry out its protein synthesis, fat synthesis, growth, maintenance of transparency and other qualities, any disruption in this process could lead to opacification. The question of the influence of hormonal regulators cannot be discussed because of lack of experimental data.

Experimentally, in rats, levels of galactose can be produced in the blood that lead only to changes in the lens, other organs showing no ill effects. The objection has been raised[45] that experimental galactose cataracts are nuclear in type, whereas in human beings nuclear cataracts are generally considered to form in the third fetal month before development of the lens is completed. Nuclear cataracts have been infrequently reported in association with galactosemia in the human infant. Their presence may imply early fetal galactosemic effects. Galactosemia in the human being has a deleterious effect on all organs, producing structural changes and altered physiology, particularly in the liver and the lens.

Sustained elevated galactose levels in the blood may also have a deleterious effect on brain tissue. In galactosemia the spinal-fluid galactose level equals that of the galactose content of the blood and implies a neurotoxic mechanism.[6] The brain injured by galactose results in permanent retardation. Brain damage by galactose in utero or a concurrent neurologic defect has been implied.[21] In 5 living patients followed,[21] 1 of whom is now eighteen years of age, all continued to show impaired galactose tolerance and mental retardation.

Treatment of galactosemia is basically the removal of milk and milk products from the diet. Lipotropic factors, such as choline and methionine, may be added. The effect of uridine phosphate, parenterally administered, in galactosemic persons may be worthy of investigation.

Summary and Conclusions

A case of galactosemia with cataracts in a six-and-a-half-year-old girl is reported.

Melituria in early infancy and childhood suggests the possibility of galactosemia, and its identity should be confirmed by appropriate tests, including paper chromatography.

The physiopathological aberrations may be due to direct toxic action by galactose on the cells or, more probably, to interference with availability of glucose for proper cell metabolism.

The normal metabolism of galactose is not clear. Available knowledge indicates the fault in galactosemia to be in the conversion of galactose-l-phosphate to glucose-l-phosphate.

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RISK OF PARALYTIC AND NONPARALYTIC FORMS OF POLIOMYELITIS TO HOUSEHOLD CONTACTS IN NONEPIDEMIC YEARS*

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A RECENT study on multiple household cases of poliomyelitis revealed a significant relation between the type of disease observed in the first member to be affected and the subsequent occurrence of clinical infection among other persons in the family.[1] It was found that the probability that subsequent cases in the family would be paralytic was greater when the initial case was paralytic than when it was nonparalytic.

The results obtained under epidemic conditions prevailing in the 1949 outbreak posed the question of whether a similar phenomenon occurred in nonepidemic years. Accordingly, the available data on household members in families having a reported case of poliomyelitis were analyzed.

The data presented below are based on the cases reported in New York City from 1950 to 1953, inclusive. All the cases were investigated by diagnosticians of the Department of Health shortly after notification, to confirm the diagnosis and to obtain relevant epidemiologic information. Only cases with an acute febrile onset and objective symptoms of involvement of the central nervous system, such as muscular weakness in paralytic cases and cervical rigidity and increased spinal-fluid cell count in nonparalytic cases, were considered as poliomyelitis.

TABLE 1. *Cases and Mortality of Poliomyelitis.*

YEAR	CASES		DEATHS	
	NUMBER	RATE PER 100,000	NUMBER	CASE MORTALITY
				%
1950	1064	13.1	64	6.0
1951	555	6.8	20	3.6
1952	821	10.2	28	3.3
1953	677	8.5	30	4.4
Totals	3117		142	
Averages		9.9		4.6

Table 1 shows the numbers of reported cases and deaths from poliomyelitis. During the four nonepidemic years under consideration, the incidence fluctuated between 6.8 and 13.1 per 100,000, and the average case mortality was 4.6 per cent. About 63 per cent of the cases reported were classified as paralytic, and 37 per cent as nonparalytic. Almost the

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same proportion was observed in the epidemic of 1949 — 62 per cent and 38 per cent, respectively. However, the case rate in the 1949 epidemic was 31.0 per 100,000 total population, and the case mortality was 7.3 per cent.

The decreased incidence of the disease in the years after the 1949 epidemic was concomitant with a drop in the frequency of multiple household infections. In the epidemic year multiple infections occurred in 4.4 per cent of the afflicted families as against 2.7 per cent of the households affected between 1950 and 1953. A summary of the occurrence of multiple cases in the nonepidemic years is presented in Table 2.

Thus, multiple cases occurred in 82 of the 3028 household units known to have been afflicted with the disease during the four nonepidemic years after 1949.

For the purpose of the study it was essential to differentiate those initially and those subsequently affected in a family. The terms "initial" and "subsequent" were preferred to "primary" and "secondary," because infection of many household members may be demonstrable by the time the first case is recognized or shortly thereafter and the source of infection is unknown.[2-5] Under these conditions, the term household "contacts" was used to denote those individuals in the family unaffected at the time of occurrence of the initial case.

TABLE 2. *Multiple Cases of Poliomyelitis in Nonepidemic Year.*

Cases per Family	No. of Cases	Percentage
1	2946	97.3
2	77	2.5
3	3	0.1
4	2	0.1
Totals	3028	100.0

In 7 cases the same date of onset was recorded for the cases observed in the family. In 5 of these households, the history was rechecked to establish which was the first case. In 2 families, however, the differentiation could not be made. Each of these families had 2 nonparalytic cases that were considered as occurring simultaneously. They had to be excluded in comparisons of initial and subsequent cases and in calculation of the "subsequent attack rate," which was defined as the frequency of poliomyelitis among household members after the occurrence of the first case of clinical infection in the family.

During the four nonepidemic years studied a total of 167 multiple cases were considered in 80 households. The cases were grouped by their sequence of occurrences in the family into 80 initial and 87 subsequent cases. The clinical types of illness observed are shown in Table 3. On the whole, there tended to be proportionately more nonparalytic types among subsequent cases than initial ones. Although the difference was not considered statistically significant for the sample size studied it was consistent with that observed in the 1949 epidemic.

The foregoing differences between initial and subsequent cases were dependent on the type of clinical infection first occurring in an afflicted family. The relation between the clinical types of initial and subsequent cases is shown in Table 4. Thus, if the initial case was nonparalytic, about three fourths of the subsequent cases were nonparalytic. Contrariwise, if the initial case was paralytic, three fourths of the subsequent cases were paralytic. These results were similar to those observed during the epidemic period of 1949.

TABLE 3. *Types of Illness in Initial and Subsequent Cases.*

Clinical Type	Initial Cases		Subsequent Cases	
	Number	Percentage	Number	Percentage
Nonparalytic	33	41.3	41	47.1
Paralytic	47	58.7	46	52.9
Totals	80	100.0	87	100.0

The clinical differences described above were obviously reflected in the fatal outcome of infection among the 87 subsequent cases under consideration. There were 11 deaths (12.6 per cent) in the entire group of 87 cases. Of these, 10 (21.3 per cent) were among the 47 cases occurring after the initial paralytic case, and 1 (2.5 per cent) among the 40 cases that followed an initial nonparalytic case. Comparable results were observed in the 1949 epidemic.

TABLE 4. *Relation between Clinical Types of Initial and Subsequent Cases.*

Type of Initial Case		Nonparalytic Subsequent Cases		Paralytic Subsequent Cases	
	Totals	Number	Percentage	Number	Percentage
Nonparalytic	40	31	77.5	9	22.5
Paralytic	47	10	21.3	37	78.7
Totals	87	41		46	
Averages			47.1		52.9

From the foregoing data it seems clear that the clinical outcome of household infection in the first member to manifest symptoms may be of some aid in forecasting the outcome of familial infection not only in epidemic periods but also in nonepidemic years.

The data described above were also considered on an age-specific basis in an effort to measure the likelihood of clinical infection for various age groups in afflicted households after the onset of a case of poliomyelitis. For this purpose it was necessary to tabulate by age the number of household members living in the house at the time a case of poliomyelitis occurred.

A total of 13,731 individuals were so recorded in the 3028 afflicted families under study. Table 5 shows the age distribution and the number affected initially in each age group.

TABLE 5. *Age Distribution and Number Affected Initially.*

AGE	INDIVIDUALS IN HOUSEHOLD		
	TOTALS	NO. AFFECTED INITIALLY	NO. NOT AFFECTED INITIALLY
yr.			
0-4	2,408	767	1,641
5-9	2,304	968	1,336
10-14	1,347	513	834
15-19	820	298	522
20-39	4,424	447	3,977
40 & over	2,428	37	2,391
Totals	13,731	3,030	10,701

The outcome of familial exposure among those not affected initially depended on the age of the contact and the clinical type of infection of the first household member to contract the disease (Table 6). When the initial case was paralytic the rate of subsequent paralytic cases among household members was greater than that of nonparalytic cases in every age group. When the initial case was nonparalytic the attack rate of nonparalytic poliomyelitis was greater than that of paralytic cases in age groups under fifteen and not significantly different in older patients.

TABLE 6. *Subsequent Cases in Household Members by Age and Clinical Type of Disease.*

AGE	HOUSEHOLD MEMBERS NOT AFFECTED INITIALLY	HOUSEHOLD MEMBERS AFFECTED SUBSEQUENTLY		PARALYTIC SUBSEQUENT CASE		NONPARALYTIC SUBSEQUENT CASE	
		NUMBER	CASE RATE PER 1000	NUMBER	CASE RATE PER 1000	NUMBER	CASE RATE PER 1000
yr.							
Initial case paralytic:							
0-4	1,061	10	9.4	8	7.5	2	1.9
5-9	802	20	24.9	13	16.2	7	8.7
10-14	451	5	11.1	5	11.1	0	0.0
15-19	320	3	9.4	2	6.3	1	3.1
20-39	2,551	8	3.1	8	3.1	0	0.0
40 & over	1,465	1	0.7	1	0.7	0	0.0
Totals	6,650	47		37		10	
Averages			7.1		5.6		1.5
Initial case nonparalytic:							
0-4	580	9	15.5	2	3.4	7	12.1
5-9	534	14	26.3	2	3.8	12	22.5
10-14	383	12	31.4	2	5.2	10	26.2
15-19	202	2	10.0	1	5.0	1	5.0
20-39	1,426	2	1.4	1	0.7	1	0.7
40 & over	926	1	1.1	1	1.1	0	0.0
Totals	4,051	40		9		31	
Averages			9.9		2.2		7.7
Initial case both types:							
0-4	1,641	19	11.6	10	6.1	9	5.5
5-9	1,336	34	25.4	15	11.2	19	14.2
10-14	834	17	20.4	7	8.4	10	12.0
15-19	522	5	9.6	3	5.8	2	3.8
20-39	3,977	10	2.5	9	2.3	1	0.2
40 & over	2,391	2	0.8	2	0.8	0	0.0
Totals	10,701	87		46		41	
Averages			8.1		4.3		3.8

Of greater interest, perhaps, is the comparative risk of subsequent paralytic infection among household members in families initially afflicted with paralytic as against nonparalytic forms of disease. This type of comparison is made in Figure 1 by age group of household contacts. In the age groups under fifteen, the risk of the paralytic form of infection was two to four times greater after a case of paralytic poliomyelitis than after a case of nonparalytic poliomyelitis. Over fifteen years of age, the differences were not statistically significant for the limited data available. Similarly, the risk of nonparalytic poliomyelitis was several times greater in households with an initial nonparalytic case than with a paralytic case for contacts under fifteen years of age, and not statistically significant for those fifteen years and older (Fig. 2).

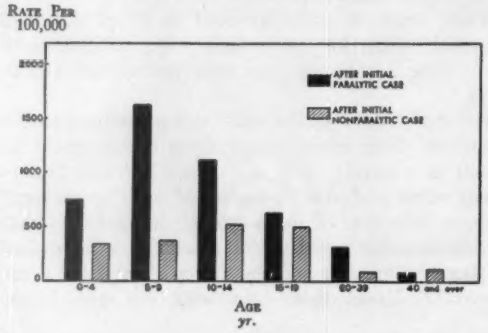

FIGURE 1. *Comparative Risk of Paralytic Infection among Household Members after an Initial Paralytic or Nonparalytic Case in Nonepidemic Years.*

When compared with the prevalence of poliomyelitis in the general population, the rate of paralytic infection among household contacts was about seventy times greater and that of nonparalytic infection a

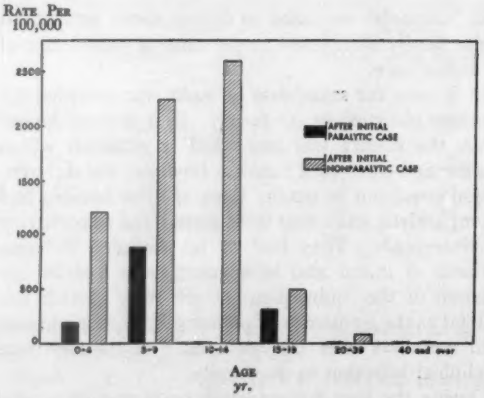

FIGURE 2. *Comparative Risk of Nonparalytic Infection among Household Members after an Initial Paralytic or Nonparalytic Case in Nonepidemic Years.*

hundred times greater. In 1949 these rates were about forty times greater than those observed in the general population. Thus, the relative increase appeared to be more marked in endemic years than in epidemic years for both paralytic and nonparalytic cases. This was due, in part, to a relatively lower attack rate in the general population than in the household contacts during the endemic years.

Discussion

The primary objective of the study was to determine the probability of clinical infection among household members after the occurrence of poliomyelitis in a member. This problem arises in every household afflicted with the disease. The questions asked usually refer to the chances that another case will develop among unaffected household members and the likelihood of the occurrence of paralysis in those subsequently affected.

Data bearing on these problems have been collected in New York City since 1949. The results obtained in the 1949 epidemic were reported previously.[1] The data obtained in the succeeding nonepidemic years are described in the present communication. The findings indicate that the probability of additional paralytic and nonparalytic cases among household members after the onset of the first case in the family is related to the clinical type of disease in the initial case and to the age of the unaffected household members. The same results were observed in the epidemic of 1949. They presumably reflect a similarity in conditions within the household conducive to the same broad types of clinical infection among household members. The precise explanation for the results obtained is not known.

The clinical observations reported are of prognostic significance in an epidemic or nonepidemic period. They indicate that paralytic disease is more likely to occur among household members when the initial case is paralytic than when it is nonparalytic. The results refer to the probability of such occurrences under certain conditions. They should be interpreted to mean not that paralysis does not occur in families after the onset of a nonparalytic case but that the likelihood of the occurrence is less for such family members than for those associated with an initial paralytic case.

Of epidemiologic interest were some of the differences between the results observed in epidemic and nonepidemic periods. When compared with the rate in the general population, the rate of clinical infection among household contacts in nonepidemic years was relatively greater than that in the 1949 epidemic period. This was true of paralytic and of nonparalytic cases.

The reliability of clinical diagnosis is a factor in every study, even one limited to paralytic cases.[6,7] The chances of error are increased for nonparalytic cases, particularly in nonepidemic years. Since clinical differentiation is difficult in nonparalytic forms of the disease an acute onset with fever, cervical rigidity and increased white-cell count of the spinal fluid were required as the minimal criteria for the diagnosis. The paralytic cases had to have evidence of muscle weakness. The clinical findings in all reported cases were confirmed by experienced diagnosticians of the Bureau of Preventable Diseases of the New York City Department of Health. The diagnosis could not be confirmed in about 20 to 25 per cent of all reported cases, and such cases were excluded from the study.[8] Serologic and cultural data were not available. The value of the application of such laboratory data in differential diagnosis has not yet been established because of the many subclinical infections and carriers in the exposed population. The utility of such laboratory methods has now been further complicated by the mass use of specific viral vaccine and gamma globulin. The elevated titers after immunization probably interfere with the serologic test for natural infection. Similar difficulties have been encountered in studies of influenza.[9]

The introduction of tissue-culture methods has made it possible to do large-scale comparative cultural studies that may be of aid in the interpretation of the epidemiologic data described in the present report. Thus far, comparative studies have not shown any association between the three known specific types of poliomyelitis virus and the severity or clinical type of disease. However, the percentage of virus isolations has been uniformly greater in paralytic than in nonparalytic cases.[10-12] In addition, stools from patients with paralytic poliomyelitis generally yielded larger concentrations of virus than those from patients with nonparalytic infection or those with transient paralysis.[13] These laboratory findings reveal differences in virus output that may have some bearing on the clinical results described in the present study.

The occurrence of a high rate of nonparalytic poliomyelitis in households where the first case is nonparalytic raises a question of the reliability of the clinical diagnosis. It is possible, of course, that a certain number of cases are caused by agents immunologically unrelated to known types of poliomyelitis virus.[14] A wide variety of such agents has been recovered from the stools of nonparalytic cases that differ from known poliomyelitis strains.[12,15-19] However, similar results have been reported for paralytic cases.[16] Until more is known of the natural distribution in health and disease of the many presently untypable strains, their role as causative agents of nonparalytic and paralytic disease simulating poliomyelitis will remain obscure.

Summary

The probability of clinical infection among household members after the onset of poliomyelitis in the family was studied in New York City during the nonepidemic period of 1950-1953, inclusive.

The data examined were obtained from an in-

vestigation of 3028 household units in which 1 or more cases of poliomyelitis occurred during the four-year period of observation. Multiple cases were reported in 2.7 per cent of these households.

The probability that paralytic infection would develop in household members after the onset of a case in the family was greater when the initial case was paralytic than when it was nonparalytic. On the other hand the risk of subsequent nonparalytic infection seemed to be greater when the initial case was nonparalytic. These differences were most striking among household members under fifteen years of age.

The attack rate among household members after the occurrence of the first case compared to that observed in the general population was greater in the nonepidemic years of 1950-53 than in the epidemic of 1949.

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RECURRENT PSYCHOSIS ASSOCIATED WITH LIVER DISEASE AND ELEVATED BLOOD AMMONIA*

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BOSTON

An increasing body of evidence suggests that ingestion of dietary protein or some other nitrogenous substances may, under certain conditions, precipitate hepatic coma or impending hepatic coma.[1-3] Adams and Foley[4] and Foley et al.[5] have detailed the clinical and laboratory signs of impending hepatic coma. These include a "flapping tremor," electroencephalographic abnormalities and changes in mental status, chiefly "reduction of awareness, followed by a brief period of quiet delirium" progressing to stupor.[5] The blood ammonia nitrogen level may be elevated.[1-3] The changes in mental function reported after protein administration have usually been transient and reversible.

In the case reported below the patient was admitted to the hospital because of confusion and manic behavior of more than a month's duration. An end-to-side portacaval shunt had previously been performed because of massive bleeding from esophageal varices secondary to hepatic cirrhosis. While psychotic he showed an elevated blood ammonia nitrogen level and a distinctly abnormal electroencephalogram. On severe protein restriction the ammonia nitrogen level fell, the electroencephalogram changed toward normal, and the mania and confusion disappeared.

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Case Report

W.B., a 64-year-old man, was admitted to the Boston Psychopathic Hospital on August 18, 1954. During the previous 5 weeks, he had been increasingly overactive, grandiose, deluded, confused and assaultive; for at least 2 weeks he had been incontinent.

The past medical history was of interest. In 1934 he began to complain of numbness and increased sensitivity of both feet. Two years later a diagnosis of pernicious anemia with subacute combined sclerosis was made; achlorhydria, macrocytosis, decreased position and vibration senses in the toes and mild spasticity of the legs were demonstrated. He had received parenteral injections of liver extract or vitamin B_{12} or both at least once every other week. He continued to complain of foot pains and leg weakness and consumed increasing quantities of wine. From 1950 until 1954 he was repeatedly hospitalized for hematemeses. Esophageal varices were diagnosed from x-ray studies, and a punch biopsy of the liver was reported to show portal cirrhosis. At the time

of admission to the New England Center Hospital for portal decompression he was pale and mildly icteric. The spleen and liver were enlarged to palpation. Vibration sense was absent in the toes and present at the ankles and above. There was moderate weakness and spasticity of both legs. The Romberg test was positive. There was a small urinary residuum after voiding. He appeared alert, garrulous and oriented. Examination of the blood showed a hemoglobin of 10.8 gm., a bilirubin of 2.5 mg. and a total protein of 6.8 gm. per 100 cc., with an albumin-globulin ratio of 0.74. The prothrombin time was 28 per cent of normal. Extensive tests disclosed normal function of the right kidney; the left had been removed in 1926 because of hydronephrosis.

He was prepared for operation, and on April 12 an end-to-side shunt between the portal vein and vena cava was performed. The portal pressure was equivalent to 30 cm. of saline solution before and 15 cm. after anastomosis. A liver biopsy showed changes compatible with portal cirrhosis or chronic infectious hepatitis.

Three weeks after operation he became drowsy and listless. Ammonium chloride had been given on the previous day. Drowsiness increased, and he appeared disoriented, confused and incontinent. Three days after the onset of drowsiness the blood ammonia nitrogen was 256 microgm. per 100 cc.* An identical level was found on the following day. Five days after onset responsiveness increased; the blood ammonia nitrogen was 171 microgm. per 100 cc. He gradually became alert, and over the next week the ammonia nitrogen fell to 108 microgm.

Two weeks later, while receiving high-protein feedings and no ammonium chloride, he again became drowsy and lethargic. The blood ammonia nitrogen was 183 microgm. It remained at this level for 6 days. He did not become disoriented or incontinent. After recovery, repeated determinations over a month's time disclosed blood ammonia nitrogen levels ranging between 85.5 and 128.0 microgm. per 100 cc. His behavior was not remarkable during that period.

He was discharged from the New England Center Hospital with instructions for a high-protein diet and 1500 cc. of fluid daily. A practical nurse who remained with him at home carefully implemented these instructions. Three weeks after discharge he again became drowsy and after recovery from stupor appeared restless and confused. The restlessness and confusion increased during the 5-week period before admission to the Boston Psychopathic Hospital. He slept little and was increasingly talkative, grandiose and forgetful. His irritability erupted frequently into threatening abusiveness. He remained demandingly loyal to his diet, fluid restrictions and vitamin instructions. He became deluded and incontinent.

On admission he exhibited flight of ideas and overactivity. His mood oscillated between despair and elation. He talked loudly and rapidly of grandiose schemes and was distractible. There were delusions of omnipotence and contact with other planets. Possessive and unkempt, he was threatening and generally disoriented. He stated that he had been hospitalized to save his life by an operation. For brief periods he knew where he was and could answer appropriately. He dressed and fed himself.

He appeared thin and weak. The blood pressure was 100/60. The temperature was 98°F. by rectum, the respirations 18, and the pulse 90 and regular. A resting tremor was present in both hands and arms, more marked on the right. No postural tremor was noted. There was no aphasia or reflex imbalance. The details of the physical examination were unchanged from those of the previous hospitalization. The central area of the tongue was well papillated, and the edges were smooth. The nail lunulae were prominent.

The family denied that the patient had had similar episodes in the past. He had been a successful street-railway engineer and executive before the onset of pernicious anemia and since then had done part-time work at home, living with his wife and 2 daughters. They described him as previously meticulous, hardworking, irritable, domineering and of good judgment. A daughter had been hospitalized in the Boston Psychopathic Hospital for an acute psychotic reaction, diagnosed as schizophrenia.

*The method used was that of Conway as modified by McDermott and Adams.[3] Three control determinations gave results of 56, 55 and 45 microgm. per 100 cc.

Examination of the blood disclosed a hematocrit of 38 per cent, a hemoglobin of 11.0 gm. per 100 cc. and a white-cell count of 5050. The urinary sediment contained many white cells; there was no albumin or sugar. The serum nonprotein nitrogen was 38 mg., and the bilirubin 1.6 mg. direct and 4.1 mg. total per 100 cc. The fasting blood sugar was 112 mg., and the total protein 6.8 gm. per 100 cc., with an albumin-globulin ratio of 0.55. Thymol turbidity was 5.8 units, and the cholesterol 258 mg. per 100 cc., with 56 per cent esters. The prothrombin time was 53 per cent of normal. The blood Hinton reaction was negative. X-ray studies of the skull and chest were negative, as was examination of the spinal fluid. The blood ammonia nitrogen was 236 microgm. per 100 cc.†

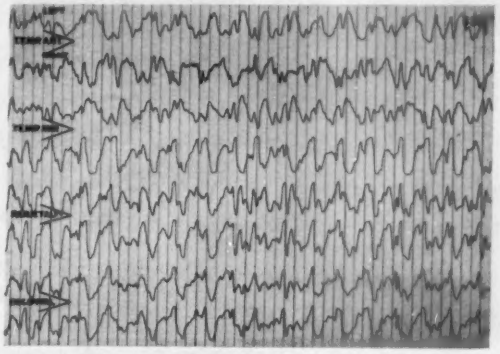

FIGURE 1. *Electroencephalogram Taken at the Height of the Psychosis (the Blood Ammonia Nitrogen Level Was Elevated).*

The high-protein diet was continued for 1 week. Agitation increased; the patient became denudative, and was incontinent of urine and feces. Intravenous feedings of glucose, water and vitamins, with supplements of fruit juice, were begun. An electroencephalogram showed diffuse high-amplitude slow waves in the range of 1 to 8 per second, mostly 1 to 3 per second, with a great deal of slow spike and wave formations repeatedly and with a definite predominance over the whole right side, especially the right temporal and parietal areas (Fig. 1). His behavior and mental state were unchanged. A day later he appeared less agitated, but remained deluded and incontinent. The blood ammonia nitrogen was 136 microgm. per 100 cc. He was then placed on a diet that consisted largely of fruits and contained less than 10 gm. of protein daily. He also received a multivitamin preparation each day and liver extract once a week. Ten days after the low-protein diet had been begun he was less often incontinent, and his rational periods were longer and more frequent. The blood ammonia nitrogen was 104.4 microgm. per 100 cc. The electroencephalogram had changed considerably: it was now a tracing of medium to low amplitude consisting of irregular, mildly slow waves of 3 to 8 per second and fast cycles of 18 to 22 per second. On 2 occasions, the slow activity was more prominent from the right parietal area than from the left. For 4 days, he had been receiving sulfaguanidine, about 2 gm. daily. He was then changed to oxytetracycline, receiving about 1.5 grams daily.

He gradually improved, becoming more co-operative and coherent. After 18 days on the low-protein diet, he was oriented and continent, dressing himself and giving sensible directions for the management of his affairs at home. Flight of ideas and overactivity were no longer present, and he did not express any delusions. He remained irritable and domineering. The blood ammonia nitrogen was now 101 microgm. per 100 cc. An electroencephalogram showed occasional diffuse, high-amplitude, synchronous bursts of 3 or 4 per second that were correlated with brief periods of drowsiness (Fig. 2). The blood bilirubin was 0.6 gm. direct and 2.5 mg. total per 100 cc. Shortly afterward the dietary

†Laboratory and technic were the same as those used in the earlier determinations.

protein was raised to 35 gm. daily, and the oxytetracycline was stopped. The urinary sediment was clear of white cells.

He was discharged on the 35th hospital day. He had been caring for himself, with little assistance, on an open ward. The family now found his attitudes and behavior essentially as they had been before the psychotic episode. A final electroencephalogram disclosed a tracing only mildly abnormal, consisting of mildly slow waves of 7 or 8 per second and a medium amplitude and sharp contour and noted in all areas, mixed with fast cycles of 15 to 20 per second. There was no localization (Fig. 3).

On discharge, he had been told to resume a high-protein diet at home. He did this with enthusiasm. On the day

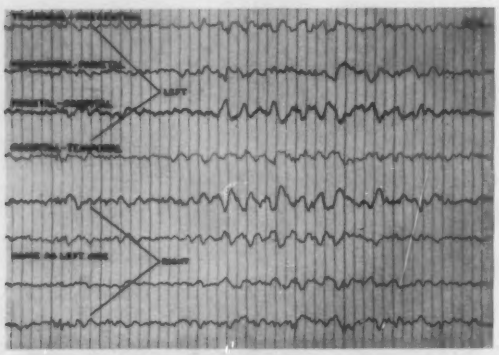

FIGURE 2. *Electroencephalogram Taken When the Psychosis Was Improving.*

The blood ammonia nitrogen level had fallen. At the time of the recording the patient was drowsy.

after discharge he appeared quieter and became drowsy, and that evening was in coma. He was readmitted to the New England Center Hospital. On intravenous glucose feedings, he was again responsive in 2 days. Over the next 2 weeks he appeared hypomanic. The blood ammonia nitrogen during this period was 154 microgm. per 100 cc. The hypomania gradually disappeared. He received throughout this admission a low-protein diet. This was continued after discharge, and he has remained for 5 months without coma or psychosis.

DISCUSSION

It is probable that the psychosis was related to the liver disease and protein intake. The electroencephalographic changes suggested those described by Foley, Watson and Adams[5] and resolved with clinical improvement. The blood ammonia nitrogen levels were elevated and later fell, though before the psychosis cleared. The presence of severe liver disease, probably portal cirrhosis, was well established. On a carefully supervised high-protein diet at home the mental changes began and progressed; in the hospital, with continuance of a high-protein diet, the patient's mental state deteriorated further. On severe protein restriction and antibiotics he improved, and maintained the improvement. Later, again while taking large amounts of protein, he became comatose, recovered while receiving nonprotein feedings and passed through a two-week period of hypomania. On continued protein restriction, without antibiotics, he has remained nonpsychotic for five months.

Both episodes of psychosis followed periods of reduced consciousness — in the second, deep coma. The first time, on continued high-protein feeding, hypomania progressed to mania, and he became incontinent. In both episodes, after protein restriction, the psychoses cleared in about two weeks.

We cannot assess exactly the relative importance of protein restriction and antibiotics. Certainly, alterations in the bacterial population of the intestines may affect the amounts of ammonia collected by the portal system. And recovery from hepatic coma has been reported after antibiotic treatment.[6,7] In any event the patient under discussion has remained free of psychosis on protein restriction alone.

The possible role of the portacaval shunt in the coma and psychoses is suggested by McDermott and Adams[2] in a report of a patient with an Eck fistula who underwent periods of change in consciousness related to ingestion of protein and certain other nitrogenous substances; these mental changes greatly diminished on protein restriction and antibiotics. It may be that the blood shunt was important in the case presented above or that the operation permitted survival at a level of liver function in which protein detoxification is greatly impaired. Certainly, the blood ammonia level, as others have reported,[8] did not reflect very accurately the patient's clinical state.

The mental changes described were of longer duration than and different character from those previ-

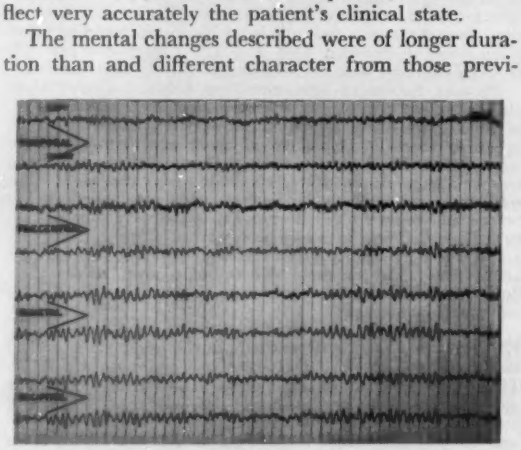

FIGURE 3. *Electroencephalogram Taken at the Time of Discharge.*

ously reported with hepatic coma. There may have been several sources of the patient's increased susceptibility to psychosis. A familial tendency was suggested by a daughter's earlier hospitalization for an acute psychotic reaction. Another source may have been brain damage, perhaps resulting from the long alcoholism or from the pernicious anemia and subacute combined sclerosis, untreated for at least two years. It is possible, too, that psychotic reactions are a more common feature of liver failure than has been reported.

SUMMARY

The case of a patient with severe liver disease and a portacaval shunt who became psychotic while re-

ceiving high-protein foods is reported. Accompanying the psychosis was an elevated blood ammonia nitrogen and an abnormal electroencephalogram. On protein restriction and antibiotics the ammonia nitrogen level fell, the electroencephalogram changed toward normal, and the psychosis, of six weeks' duration, cleared. Again on high-protein foods and after a period of coma, the psychosis recurred.

We are indebted to Mrs. R. Mayo, of the Surgical Research Laboratory, New England Center Hospital, who did the blood ammonia nitrogen determinations, and to Dr. Milton Greenblatt, of the Boston Psychopathic Hospital, who interpreted the electroencephalograms.

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MEDICAL PROGRESS

ENDOSCOPY (Continued)*

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Boston

Esophagoscopy

Physiology

Sanchez, Kramer and Ingelfinger[78] have studied motor phenomena of the esophagus with pressure-recording apparatus and simultaneous fluoroscopy. In the upper seven eighths of the esophagus the swallowing complex consists of two major components: an immediate, slight elevation of pressure, corresponding to the injection of oral contents into the esophagus, and a later, higher pressure wave produced by peristaltic contraction of the esophageal lumen. During repeated swallowing, the peristaltic pressure wave is inhibited until after the last swallow. In the distal esophagus two different types of swallowing complexes are found. These occur in the anatomic regions labeled by Lerche as the ampulla and the vestibule. In the ampulla the pressure created by peristalsis falls off more gradually than in the upper esophagus. The initial pressure rise that follows immediately on swallowing is not transmitted into the vestibule, and the usual peristaltic pressure wave does not occur in this area. It is suggested that the distinct motor phenomena of the distal esophagus may play a part in the benign clinical disorders affecting this area.

Esophagitis

Ripley, Olsen and Kirklin[79] state that of 65 patients who underwent esophagogastrostomy or cardioplasty, 28 subsequently had positive, and 12 presumptive signs of peptic esophagitis or formation of stricture. No conclusions about the frequency of these complications can be drawn from these data, because of the mode of selection of cases. The very fact that they occur at all is of utmost importance, and must act as a stimulus to the development of technics that will tend to prevent them.

Winkelstein et al.[80] have studied 20 cases of peptic esophagitis, of which 15 were associated with simultaneous duodenal ulcer and 2 with gastric ulcer. They found that surgical therapy was not as successful as medical therapy combined with bougienage. Four patients had had previous gastric operations. The cause of the esophagitis seemed to be the regurgitation of acid and pepsin into a lower esophagus with a susceptible mucosa. Ectopic gastric secretory tissue was not found in this series.

Carver and Sealy,[81] in a discussion of peptic esophagitis, found that of 101 patients in whom esophagoscopy was performed, 82 had evidence of acute or chronic ulceration. Elevation of the head of the patient's bed on 8-in. (20-cm.) blocks is essential in preventing gastric reflux and should be a permanent part of the therapeutic program. Most patients with peptic esophagitis can be treated successfully by medical measures; however, patients must continue prophylactic treatment to prevent recurrence with esophageal shortening and, ultimately, stenosis.

Benedict and Gillespie[82] reviewed the literature on esophageal stenosis caused by peptic esophagitis or ulceration. They concluded that peptic stenosis of the esophagus is due to abnormally prolonged contact of gastric juice with the region above the cardia. Peptic stenosis can occur in a normal person, but it more probably occurs in patients with the ulcer diathesis. Gastric juice is present in the lower esophagus

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to an abnormal extent as the result of the following factors: esophageal hiatus hernia of the sliding type; and excessive vomiting or regurgitation from relaxation of the cardia. Esophagitis is present in all cases, and almost half the patients have evidence of ulceration. Bougienage, after the swallowing of a thread, is satisfactory in most cases. Surgical treatment is necessary in cases of excessive bleeding and failure to respond to bougienage and when there is risk that an ulcer will perforate.

Brackney and his associates[83] made studies to determine the frequency of esophagitis in dogs after the two standard procedures for the treatment of mega-esophagus — namely, the Heller and Wendel operations. Mongrel dogs were employed. The Heller operation consists of an extramucous myotomy of the esophagogastric junction. The Wendel procedure consists of a longitudinal incision through all layers of the esophagogastric junction, which is closed transversely. The authors conclude that dogs subjected to the Wendel operation for mega-esophagus developed severe esophagitis, whereas dogs with the Heller operation did not. Vagotomy and pyloroplasty together were effective in preventing esophagitis in dogs with the Wendel procedure receiving histamine injections.

Watkins, Prevedel and Harper[84] have described a method of preventing peptic esophagitis after esophagogastrostomy. The technic of valvular esophagogastrostomies is described and illustrated. Valvular esophagogastrostomies were carried out in dogs in which the entire stomach pouch was preserved. These dogs survived without evidences of appreciable esophagitis for periods varying from sixty-three to two hundred and thirty-four days, and were still living at the time of this report. This procedure has been carried out in human patients with encouraging clinical and roentgenologic results. It has the advantage of being applicable to both high and low esophagogastrostomies.

Hiatus Hernia

Sweet[85] analyzed 130 cases of hiatus hernia treated surgically. In all patients, the hernia was repaired through a transthoracic approach. The majority experienced complete and permanent relief from symptoms. In no case has there been any recurrence of bleeding. Four proved recurrences of the hernia have been observed (a rate incidence of 3 per cent).

Flood, Wells and Baker[86] state that hiatus hernia is frequently accompanied by ulcerative esophagitis. Esophageal reflux was demonstrated by radiologic or intubation technics in more than half their patients with hiatus hernia. Acid reflux was found in patients both with and without evidence of esophagitis.

Esophageal Ulcer

Nardi[87] reports a case of perforation of the aorta by a benign esophageal ulcer, with fatal hemorrhage. Though such perforations secondary to malignant ulcer are not uncommon, spontaneous esophagoaortic fistula secondary to a peptic ulcer of the esophagus has not previously been described. The pathogenesis of this complication is understandable in the light of pathological studies on perforation of the aorta by esophageal carcinoma, as well as the anatomic findings in the patient.

Wolfson and Greenberg[88] presented a case of chronic acetanilid poisoning in which an esophageal ulcer developed. They believed that this hitherto undescribed complication might be ascribed to the chronic ingestion of acetanilid.

Haubrich[89] found 5 cases of ulcer of the esophagus in a series of 25 patients with severe kyphoscoliosis, all lesions being located in the middle third of the esophagus. He said that ulcers high in the esophagus are extremely rare and can be explained only by marked kinking of the esophagus in kyphoscoliosis. Peptic digestion of the wall of the esophagus might play some part. Also, aberrant islets of gastric mucosa have to be considered. The etiology of ulcers of the esophagus in kyphoscoliosis is probably complex, and the significance of individual factors is uncertain. The unusually high frequency suggests some relation to angulation of the esophagus and to a *locus minoris resistentiae*. The increased mechanical strain, the topographically distributed disturbances in the blood and nerve supply, the digestion by aberrant gastric mucosa or ascending gastric juice because of cardial disturbances and esophagitis with closure of the cardia may all contribute to render the ulcers more frequent than usual and account for their atypical location in kyphoscoliosis.

Sweet and his associates[90] have described 30 men and 20 women with peptic ulceration and stricture of the lower esophagus who were operated upon. The evidence presented bears out the impression that surgical measures should never be delayed in any case of ulcer or stricture of the esophagus in which there is a history of bleeding, obstruction unsuccessfully treated by bougienage, intractable pain or, in some cases, evidence of perforation. If a careful choice of operative procedure is made to suit the conditions encountered and the age and physical status of the patient, a satisfactory clinical result can be anticipated in at least 90 per cent of the patients. A diagnosis of recurrent esophagitis after operation can be established only on the basis of roentgenologic and esophagoscopic examination, but the definitive proof of the diagnosis depends on the use of the esophagoscope.

Benedict and Gillespie[91] studied 100 cases of peptic stenosis of the esophagus and concluded that peptic stenosis is due to abnormally prolonged contact of gastric juice with the region above the cardia. It can occur in a normal person but is more likely in those with the ulcer diathesis. Gastric juice occurs in the lower esophagus to an abnormal extent as the result of the following factors: esophageal hiatus hernia of the sliding type; and excessive vomiting or regurgita-

tion from relaxation of the cardia. Esophagitis was present in all their 100 cases, and 42 gave evidence of ulceration. In view of these findings, it is desirable to repair hiatus hernias that are causing symptoms and do not respond to other measures. In theory, gastrectomy for gastroduodenal ulcers ought to be of value in preventing the development of peptic stenosis of the esophagus, but the present series does not support this thesis. Bougienage, after swallowing of a thread, is satisfactory in most cases. It should be combined with dietetic treatment, antispasmodics and antacids. There are three indications for surgery: failure of bougienage; severe hemorrhage; and perforation.

Allison and Johnstone[92] presented records of 7 patients in whom the lower esophagus was lined by gastric mucous membrane. All the patients had reflux esophagitis, which had progressed to fibrous stenosis in 4. One of the 4 also had two gastric ulcers in the part of the esophagus lined by gastric mucous membrane, from one of which there had been profuse bleeding. Another patient had a chronic gastric ulcer in the part of the esophagus lined by gastric mucous membrane, and this not only had caused stenosis but also had penetrated the esophageal wall to produce a subacute perforation into the mediastinum. A review of the previous patients attending the clinic with peptic stenosis of the esophagus showed that the stricture was in the squamous part of the esophagus in 115 and in the gastric lining in 10. In 23 the exact pathology could not be stated with certainty.

Schatzki and Gary,[93] in a study of dysphagia due to a diaphragmlike localized narrowing in the lower esophagus ("lower esophageal ring"), found this affliction in 5 men. The greatest diameter of this diaphragm or ring is constant in a given person except that it can be slightly stretched as solid or semisolid food passes through it. The position of the ring is also constant in a given person. The constancy of the diameter of the ring is best tested with barium-filled gelatin capsules.

Holinger et al.[94] believe that the management of benign strictures of the esophagus varies according to the etiology, degree and duration of the stricture, the age of the patient and the success or failure of previous therapy. There is agreement between the endoscopic and surgical divisions at the Children's Memorial Hospital in New York City that dilatation of esophageal strictures should be continued until it becomes apparent that a functional esophagus cannot be obtained by conservative measures. Dilatations of benign strictures of the esophagus are performed in several ways, depending on the location, size and rigidity of the stricture. They may be done by esophagoscopy either by bougies inserted through the scope or by the scope itself; by Plummer bougies passed over a previously swallowed thread, by retrograde Tucker bougies in some patients after gastrostomy; by graduated mercury-filled bougies; or by pneumatic bougies correctly placed under fluoroscopic guidance.

Lye Stricture

Weisskopf[95] reports the effects of cortisone on experimental lye burn of the esophagus. A standard burn technic was used that consisted of passing a Levin tube as far as the cardia and instilling 20 cc. of 10 per cent lye into the esophagus. After a minute, the lye was washed out with 40 cc. of tap water and sucked out of the esophagus. The treated animals were placed on cortisone acetate (75 mg. a day) in two doses given intramuscularly, and oxytetracycline (500 mg. a day) given orally. Fifteen animals were used and killed over periods ranging from seven to one hundred and twenty days. The control animals continued to vomit thick secretions for several weeks, whereas the treated animals were perfectly normal at the end of a week. The control group had marked granulations, and although strictures developed in all, none were complete. Strictures were not found in the treated group, in which the granulations were much finer, when present, and there was very little evidence of inflammatory reaction. Complications as a result of the blocking of the body's response to injury by means of cortisone acetate were seldom found. Rosenberg had found the mortality rate to be twice as high from perforation and mediastinitis. Microscopical sections were made of all the animals' esophagi, and the two groups showed a considerable difference. There was a large increase in the exudation of the control group in addition to dense fibroplasia in the deeper granulations that tended to wall off the injured area.

Silk and Stempien[96] have reported the oral use of procaine in a case of Lysol poisoning. The striking success of procaine gargles and swallows in this case was very encouraging. After great distress on a liquid diet the patient immediately tolerated a full bland diet. The advantage in nutrition and hydration is obvious. The cortical steroids greatly inhibit granulations but interfere little with epithelization. In view of this action, it was considered safe to begin ACTH at once. It is believed that the plan of giving procaine by mouth to overcome dysphagia and ACTH to prevent scarring and contracture deserves a wider trial.

Web

Bingham and Logan[97] studied the nature and treatment of Plummer–Vinson dysphagia, which they consider to be due to organic stenosis — namely, web formation. There should be little difficulty in distinguishing this disease on clinical grounds from neurologic, hysterical or anxiety dysphagia. Endoscopy clinches the diagnosis. A negative barium swallow is valueless in excluding it. The most important complication is the onset of carcinoma, usually in the upper esophagus but sometimes in the lower esophagus or in the stomach. The clinical diagnosis of Plummer–Vinson disease is described. Dilatation of the stricture is the essential treatment. Plummer–Vinson disease is a precancerous condition.

Achalasia

Nemir and Hawthorne,[98] in a discussion of the physiologic basis for esophagocardiomyotomy in the treatment of achalasia, state that the results of the Heller procedure or esophagocardiomyotomy are unequivocally better than those obtained with the other procedures. Although complications have continued to occur they have been much less frequent and less severe. The authors conclude that esophagocardiomyotomy does not alter the deranged esophageal motility. The procedure probably has a beneficial effect by breaking the circus movement at the lower end of the esophagus, thereby relieving a functional obstruction and permitting better emptying. Postoperative complications are less frequent and less severe because of the fact that regurgitation is less prevalent than in the cases in which esophagogastrostomy is carried out. It is postulated that a derangement or disorganization of the intrinsic neural mechanism, rather than an absolute absence of the nerve plexuses, is responsible for the disordered motility pattern.

Barrett,[99] in a report on the etiology of achalasia, divides the disease into three phases. Radiologists state that in the first phase the esophagus, between the arch of the aorta and the cardiac sphincter, moves more actively than is usual on screening. The movements resemble peristalsis and occur in phases. There is no permanent obstruction to the passage of foods or liquids. In the second phase the patients generally consult a doctor because of dysphagia; the dominant abnormality concerns the act of swallowing. The patient often notices that the esophagus seems to contract and relax as food is taken and that, if too much is swallowed quickly, it feels distended and unwilling to accept more. The radiologic changes of the second phase, as observed on screening after a barium swallow, afford this evidence. The first mouthful often passes into the stomach if the gullet is empty at the time. After this a holdup develops in the lower 2 or 3 cm. of the esophagus. The inflammation that is often found in the mucosa of the dilated "sac" is not due to digestion by regurgitated acid pepsin, but to stagnation of food above the obstruction. In the third phase the esophagus elongates and becomes tortuous. The bulbous part sags into the right side of the chest and then crosses horizontally to the left before turning into the abdomen. Some have claimed that this type of mega-esophagus may be different from achalasia and due to a congenital abnormality. This idea is based on the fact that a number of cases of mega-esophagus, affecting the whole viscus, have been described in infants. But most people believe that the cardiac sphincter, which is at the junction of the stomach and the esophagus, below the "neck" of achalasia, is not concerned with the disease; the lower 2 or 3 cm. of the esophagus is normally smaller than the rest, and this part forms the "neck" in achalasia. It is agreed that the effects of sympathetic nerves on the movements of the esophagus are inconstant and unimportant. In achalasia both the vagi and the sympathetic nerves appear to be normal. A summary of the physiologic points suggests that achalasia in man is not due to an abnormality of the vagus nerves or the sympathetic system. In conclusion Barrett believes that achalasia is a disease of the esophagus itself: the initiating cause may be a congenital deficiency of the ganglion cells of Auerbach's plexus, a psychologic upset or a vitamin shortage. He concludes that both hydrostatic dilatation and Heller's operation are excellent treatments because they overcome the obstruction without destroying the cardiac sphincter. By contrast, plastic operations on the esophagogastric junction and esophagogastrostomy fail because, in the long run, reflux esophagitis occurs.

Butin et al.[100] studied esophageal pressures in normal persons and patients with cardiospasm. Recently, a satisfactory method that allows accurate recording of pressures in the esophagus has become available. This consists of a miniature electromagnetic transducer originally devised to record intravascular pressures and recently modified for application to the gastrointestinal tract. The transducer affords an ideal instrument for the measurement of motility after deglutition since its presence in the esophagus does not stimulate contraction. In this study, variations in pressure occurring in the esophagus both at rest and after swallowing were determined in a group of normal persons by means of the transducer. The results were then compared with those derived from a similar series of observations in a group of patients who had cardiospasm. The changes in pressure in normal persons followed a definite pattern, which consisted of an initial wave of negative pressure and three subsequent waves of positive pressure. Analysis indicated that the final positive wave was produced by a true peristaltic wave passing the transducer. Patients with cardiospasm showed considerable spontaneous motility as well as extremely variable responses in pressure as the result of deglutition. Although waves of positive pressure were noted occasionally in these patients after swallowing, a co-ordinated, distally traveling wave of the peristaltic type could not be identified.

Crenshaw and Booher[101] found 18 previously reported cases of cancer developing in achalasia of the cardia. The history of a fifty-four-year-old man with a twenty-seven-year history of achalasia in whom cancer of the lower third of the esophagus subsequently developed is added. Esophagoscopy should be a routine diagnostic procedure in achalasia of the cardia.

Olsen, Holman and Andersen[102] believed that, regardless of the role of psychiatric disturbances, cardiospasm has an organic basis. Once the disease is established they question whether much will be accomplished by psychotherapy. Cardiospasm, or achalasia, is a nonorganic stenosis of the lower end of the esophagus. This condition must be distinguished from esophageal spasm (diffuse spasm) and reflex spasm at the cardia. During a twelve-year period 601 patients

with cardiospasm were seen and treated at the Mayo Clinic. There were 327 males and 274 females. The patients varied in age from two to eighty-eight years. There were 17 children in the group who were less than fifteen years of age. In the differential diagnosis of cardiospasm carcinoma of the cardiac end of the stomach, which at times closely simulates it, is the most important condition to be considered. Esophagoscopy is usually unnecessary in making the diagnosis of cardiospasm but is sometimes desirable in the effort to exclude carcinoma. Esophagoscopy was performed 110 times in their 601 cases. Seventy-two esophagoscopic examinations were done for diagnostic purposes, and the rest to assist in the treatment.

Necheles et al.[103] believe that JB 305 (N-ethyl-3-piperidyldiphenylacetate hydrochloride), a new drug that has both spasmolytic and topical anesthetic properties and possesses such a degree of tolerance that even large doses do not cause undesirable reactions, is of benefit in the medical treatment of cardiospasm. Although they cite only 2 cases, the results obtained in these patients seem to justify therapeutic trials with JB 305 on a larger scale.

Sleisenger, Steinberg and Almy[104] studied the influence of the autonomic nervous system on the function of the human esophagus and concluded that in cardiospasm the parasympathetic stimuli to the esophagus are weak and unco-ordinated.

Diverticulum

Putney and Clerf[105] have reported 7 cases of epiphrenic esophageal diverticulum. Although the diagnosis was made by roentgenologic study esophagoscopy served to confirm the diagnosis and detect complicating lesions, at the same time providing additional information about the mucosal changes.

Maier[100] states that very few diverticula of the midthoracic esophagus cause symptoms or are of clinical significance. Occasionally, however, symptoms occur, and surgical treatment may be indicated. Not all diverticula in the region are of the traction type. An illustrative case of pulsion diverticulum is reported. Transthoracic resection completely relieved the difficulty in swallowing.

Varices

Crile[107] has discussed the rationale of transesophageal obliteration of esophageal varices and has pointed out that in patients with extrahepatic block true portal hypertension may not be present and portacaval shunts may be impracticable or useless. Radical operations, with resection of the lower esophagus and upper parts of the stomach, may be of value, but these procedures carry a high mortality and morbidity and should be avoided whenever possible. Seven patients with esophageal varices secondary to extrahepatic block of the portal or splenic vein were treated by transesophageal obliteration of esophageal varices and followed for thirty-three to forty-eight months since operation. Five had no further bleeding after operation, despite the fact that they had previously been bleeding on an average of fifteen times a year for several years and conventional methods of treatment had failed to stop the bleeding. One of the 2 patients who bled again appeared to be bleeding from a gastric ulcer, and the other, who had been bleeding at two-week intervals for several years before operation, had had no bleeding in the past two and a half years and had only experienced two small episodes in the first few months after operation.

Palmer and Brick[108] studied the sources of upper gastrointestinal hemorrhage in cirrhotic patients with esophageal varices. The observations presented imply an important warning against immediate assumption that esophageal varices are at fault when the cirrhotic patient presents himself with massive hemorrhage. An argument emerges for thorough diagnostic study under the circumstances. Wider utilization of emergency surgical procedures to halt hemorrhage from esophageal varices makes it increasingly important that the actual source of hemorrhage be determined. Forearming oneself with knowledge obtained simply by endoscopic and radiologic study of the upper gastrointestinal tract in each cirrhotic patient permits rational treatment in the event of complication.

Linton[109] states that cardioesophageal tamponade with an intragastric balloon tube, supplemented by immediate transesophageal suture of the varices, is the best emergency method of controlling the massive bleeding in these patients when it does not stop spontaneously. The great advantage of this procedure is that, once the bleeding is controlled, the patient's condition can be built up more satisfactorily with proper food and vitamins than when any other method is employed.

Brick and Palmer[110] have estimated the frequency and discussed the methods of diagnosis of esophageal varices in patients with cirrhosis of the liver. Data are presented in 150 patients with histologically proved cirrhosis in whom esophagoscopy was done as a routine procedure. Esophageal varices were found in 95 cases. A fairly high rate of varices, 52.7 per cent, was observed in cirrhotic patients who had no history of hemorrhage. The comparative diagnostic value of x-ray study in this series is indicated by the fact that only 21 per cent of the cases of varices present were diagnosed by that method. Esophagoscopy is shown to be a safe procedure, and the authors advocate routine study of all cirrhotic patients by the method.

Sullivan, Lienhard and Lukeman,[111] in a study of massive hemorrhage in patients with both esophageal varices and duodenal ulcer, state that judicious employment of esophagoscopy and gastroscopy will further increase the accuracy of diagnosis by detection of lesions not revealed by the x-ray examination and by distinguishing the actual site of bleeding in the 15 per cent of cases in which multiple lesions are present. They do not recommend the indiscriminate use of endoscopy but are convinced that skillfully per-

formed examination is safe and will on occasion provide life-saving information.

Benign Tumor

Sweet, Soutter and Valenzuela[112] have presented a series of 22 muscle-wall tumors of the esophagus. Twelve of these, 1 malignant and 11 benign, were removed surgically. Endoscopic biopsy of the lesions through an intact mucosa is seldom fruitful and potentially dangerous, and renders subsequent enucleation without contamination impossible.

Boyd and Hill[113] report on 15 patients with benign tumors of the esophagus. There were 9 leiomyomas, 2 cysts, 2 fibromas, 1 hemangioma and 1 polyp. Benign esophageal tumors can be diagnosed with assurance by means of the barium swallow and fluoroscopy. Esophagoscopy, with or without biopsy, is not necessary in many cases. A biopsy, by breaking through the mucosa, may add greatly to the risk of removal of an esophageal tumor. All the intramural tumors discussed were removed by thoracotomy, with enucleation of the tumor from the esophageal wall without incision of the mucosa and consequent entrance into the lumen of the esophagus. This would not have been possible if the mucosa had been opened by a biopsy. Esophagoscopy was performed in 9 patients, and the benign nature of these tumors was recognized by direct vision, thus eliminating the need for a biopsy. Intraluminal tumors can be removed safely through the esophagoscope with the snare and coagulating current, provided the tumor is not too large or its pedicle too broad.

In a collective review Lewis and Maxfield[114] present 46 operative and 108 autopsy cases of leiomyoma of the esophagus. They believe that symptoms and x-ray findings involving the esophagus are indications for esophagoscopy. The diagnostic value of this procedure resides in a quartet of minimal or negative findings that are astonishing in the face of the conspicuous lesion revealed by the roentgenogram. The first is a mucosa that is normal, although ulceration or congestion was seen in 3 cases; the mucosa was unaltered in all the others. The second concerns the tumor mass. The tumor bulges into the lumen in varying degree; cases with multiple tumors present multiple bulges. In a number of cases the tumor was not seen by the esophagoscopist even though it was demonstrable on the esophagram. Usually, however, the lesion was described as being in the wall of the esophagus or as extraesophageal. The third point of diagnostic value is the character of the luminal diminution. Narrowing of the lumen by the myoma is common, but obstruction to the passage of the scope and stenosis are not. Fourthly, the tumor is freely movable in most instances. Esophagoscopy is important in several respects in addition to its diagnostic value. Localization of the segment of esophagus and the sector of wall involved is possible. Often nothing can be found to biopsy, the mucosa being normal and the tumor not being visible except as a bulge. Study of the cases in this survey indicates that planned avoidance of biopsy is to be recommended. In the first place the procedure is unlikely to be diagnostic. Secondly, the practice of biopsy in myoma of the esophagus has been said to possess a strong element of danger. The only justification for biopsy is an ulcerated or suspicious mucosa or a truly intraluminal tumor. A mural bulge is not sufficient indication.

Carcinoma

Adler and Deeb[115] describe 2 cases of carcinoma of the esophagus in which autopsy, after seventeen and thirty-four months, respectively, after combined external and intracavitary radiation therapy, failed to reveal any residual tumor. Another case is reported, with a survival of twenty-five months, in which the patient gave no evidence of recurrence — clinically, roentgenologically or by esophagoscopy and biopsy. The authors believe that radiation therapy for carcinoma of the esophagus should be used more frequently. Radiation is recommended in all cases in which no operation or only incomplete surgery can be carried out. The negative attitude toward radiation therapy of cancer of the esophagus is not justified. Combined external x-ray and intracavitary radium therapy of carcinoma of the esophagus needs further investigation for complete evaluation.

Berman[116] enumerates the difficulties encountered in the treatment of carcinoma of the esophagus that induced him to study the possibility of replacing segments of the thoracic portion of the esophagus with a specially prepared polyethylene plastic tube. The experimental work was extremely encouraging in that the operative procedure was short and simple. During the last two years the method has been used in 30 patients — in 28 for neoplastic disease. The mortality was considerably less than that with conventional methods, the morbidity was negligible, and the patients were much more comfortable. In the last 15 cases in which this technic was employed, the operating time was less than an hour and a half as contrasted to four or five hours by the older technics, the anastomosis requiring approximately ten minutes. The mortality has been under 10 per cent, in contrast to 15 to 40 per cent with older methods. Leakage from the mediastinum was observed in 1 patient, but ceased in a short time. There were almost no pulmonary complications, and there was no regurgitation or other evidence of esophageal irritation in patients followed for over a year after the operation. A fibrous sheath lined with epithelium forms around the tube, which may be removed by esophagoscopic methods a few months after the operation, with little possibility of stricture. As much as 7 in. (17.5 cm.) of esophagus has been resected and replaced by the tube.

Franklin and Shipman[117] studied 159 patients with carcinoma of the esophagus. Esophagoscopy proved to be the most reliable diagnostic measure. X-ray

examination with barium swallow was helpful but was less reliable. The site of growth was the lower third of the esophagus in 60 per cent, middle third in 28 per cent and upper third in 12 per cent.

Sweet[118] states that there is further substantial evidence that in carcinoma of the midthoracic and lower esophagus, including the cardia, the operation of resection with esophagogastric anastomosis gives worthwhile palliation of distressing dysphagia. It is shown that when the cases are reclassified into those the surgeon thought curable and those he thought incurable, the results in terms of five-year survival after resection are 14 per cent for cases of carcinoma of the midthoracic segment and 34 per cent for those of carcinoma of the lower esophagus and cardia. The results with the latter group are identical whether the growth is epidermoid carcinoma or adenocarcinoma. The value of esophagectomy for carcinoma of the midthoracic and lower segments of the esophagus is emphasized.

Mackler and Mayer[119] have described a method whereby palliation of obstruction due to carcinoma of the esophagus may be achieved by the introduction of a permanently indwelling tube. The tube is surgically inserted at the time of thoracic exploration when it is determined that resection of the esophagus is not feasible. It is suggested that, because of its simplicity, the method might profitably be substituted for resection and esophagogastrostomy, in many cases, when esophagogastrostomy is performed purely for palliative purposes with no prospect of eradicating the pathologic process.

Other Malignant Tumors Involving the Esophagus

Garfinkle and Cahan[120] have reported a primary melanocarcinoma of the esophagus in a fifty-year-old woman. They believe this to be the first histologically proved case in the medical literature.

In a recent case[121] an oat-cell carcinoma of the left lower lung, with erosion of the esophagus, was presented. In addition to other symptoms the patient had difficulty retaining food and experienced nausea and vomiting. Barium-swallow examination revealed that the esophagus was widened down to a point just below the level of the aortic arch, where it showed a fusiform, stringlike narrowing consistent with extrinsic constriction. Esophageal obstruction produced by direct extension of bronchogenic carcinoma, although not very common, occurs often enough to be an important consideration in differential diagnosis.

A primary malignant melanoma of the esophagus in a sixty-year-old woman has been described by Fowler.[122] In addition to the primary tumor there were macroscopic pigmented areas adjacent to the main tumor and microscopic changes in the adjacent "normal" esophagus. The author believes that these were areas of independent proliferative change representing underlying multicentric primary changes rather than metastatic growths.

Robertson[123] has also reported a case of malignant melanoma of the esophagus with metastasis to regional lymph nodes, lungs, liver, pancreas and peritoneum. No other primary site could be discovered, and he believes that this case should be classified as a histologically proved case of primary malignant melanoma of the esophagus.

Foreign Bodies in the Esophagus

Krauss[124] states that the liquid paraffin used as a collapsing agent in a surgically prepared extrapleural space may find its way to the mediastinum and infiltrate the loose connective tissue surrounding the esophagus. The presence of oil under tension provokes an inflammatory reaction in the periesophageal tissue and sometimes results in a fibrotic sheath constricting the esophagus. Since the mucous membrane is usually not involved in this process, dilatation by bougies may be sufficient to relieve the dysphagia, but, if prolonged treatment with bougies fails to correct the stenosis, surgical intervention may be necessary.

Kergin[125] has had a similar experience and reports a case of esophageal obstruction due to mediastinal paraffinoma. Six years after paraffin oil was introduced into the extrapleural space of a patient, dysphagia due to a paraffinoma of the mediastinum developed. This paraffinoma invaded the esophagus to produce a stricture that proved refractory to prolonged attempts at dilatation. Surgical reconstruction was necessary.

Valle and Cloutier[126] have presented a case of so-called middle-lobe syndrome produced by the presence of a denture in the lower third of the esophagus. The denture was removed through a thoracotomy on the right, and the atelectasis cleared.

Esophageal obstruction due to Serutan has been reported by Melamed and Marck.[127] Serutan is a hygroscopic substance that becomes swollen and spongy on the addition of water. If an insufficient quantity of water or fluid is taken after ingestion of the hygroscopic material or if transient spasm or constriction in the esophagus occurs, the rapidly swelling mass may become trapped. In the case reported the foreign body was vomited after a second dose of mineral oil, and complete relief was obtained.

Trauma

Calenda and Uricchio[128] have reported a case of spontaneous perforation of a syphilitic aneurysm of the descending aorta into the esophagus. There was a sudden episode of hematemesis, and the patient died suddenly.

Ware, Shinder and Davis[129] state that spontaneous rupture of the esophagus occurs, as the term implies, without pre-existing esophageal disease and in the absence of a foreign body or instrumentation. The act of vomiting is intimately associated with this catastrophe. Reviewing the English literature, they found 85 cases that fulfilled the criteria for spontaneous rupture of the esophagus. Commenting on the mechanism of

rupture, the authors suggest that, particularly in patients recovering from acute alcoholism, the act of vomiting may be deranged in either or both of two ways: as a result of repeated stimuli the vomiting may become fatigued; and owing to a confused mental state, there may be poor co-ordination of the mechanism during the actual process of vomiting. The commonest symptoms are epigastric pain and vomiting. The single most valuable test is the roentgenogram of the chest. Once the diagnosis is established or suspected, thoracotomy must be done.

Mackler[130] states that spontaneous rupture of the esophagus is an accident that may follow a sudden rise in intra-abdominal pressure, usually vomiting. Other acts that have resulted in rupture are straining at defecation, lifting a heavy weight, a convulsive seizure of grand-mal epilepsy and the labor of childbirth. Distinction is made between rupture and perforation of the esophagus. The triad of vomiting, pain in the lower thorax and emphysema of the neck is diagnostic and constitutes sufficient evidence to warrant a left-sided thoracotomy. Evidence is presented to support the conclusion that rupture occurs in a previously normal, healthy esophagus as a result of intraesophageal pressure, transmitted from the stomach. The rupture uniformly occurs at the lower extremity of the esophagus on the left lateral wall, apparently the weakest part of the organ as demonstrated by experimental inflation and bursting of the esophagi of 65 fresh human cadavers. The site and configuration of the resulting rupture duplicated exactly the clinical lesion. Three cases of spontaneous rupture of the esophagus are presented. The treatment was surgical: left thoracotomy, suture of the esophagus and drainage. The recovery of 2 of the patients brings to a total of 13 those surviving a spontaneous rupture of the esophagus. The outcome was uniformly fatal before the adoption of a surgical method of treatment.

Muller, Byron and Power[131] describe 2 patients in whom rupture of the esophagus occurred several weeks after an operation had been performed on other thoracic structures. The mechanism of production and the diagnosis and treatment of these delayed traumatic perforations are discussed.

Grigsby, Brown and Cave[132] believe that it is imperative to consider spontaneous rupture of the esophagus in patients with severe epigastric or precordial pain that occurs during violent vomiting or retching. Pneumothorax and subcutaneous emphysema are frequently found on physical examination. Although the diagnosis is established only by demonstration of a communication between the esophagus and pleural cavity, strong confirmation is obtained when hydrochloric acid, vegetable material or clostridia are found in the pleural aspirant. Extensive perforation may be present without dysphagia.

Decker, Zamcheck and Mallory[133] state that although it appears that lacerations at the cardia are an infrequent cause of gastric hemorrhage this syndrome (Mallory–Weiss) undoubtedly accounts for some cases of gastrointestinal hemorrhage of otherwise undetermined origin. Eleven cases are reported. In all cases the lacerations conformed to the original descriptions of Mallory and Weiss, ranging from 0.5 to 3.0 cm. in length and up to 0.7 cm. in maximum width. Most of them involved both the distal end of the esophagus and the proximal portion of the stomach, the lesion often being nearly bisected by the cardioesophageal junction. A few lesions were confined to the stomach alone, being located immediately distal to the gastroesophageal junction, but none were limited to the esophagus alone. Moderate to severe degrees of chronic atrophic gastritis were present. The seriousness of vomiting as a symptom is emphasized by these 11 cases of gastrointestinal bleeding from lacerations at the cardiac orifice of the stomach induced by vomiting. Most of the cases of this syndrome originally reported by Mallory and Weiss were associated with alcoholism. Many of the cases in the present series, however, were associated with a variety of diseases not only in the gastrointestinal tract but also in remote organs. Protracted vomiting or retching remains the common etiologic factor in all cases. Associated pathogenetic factors include chronic atrophic gastritis, alcoholism and nutritional cirrhosis.

Russell[134] reports a case of spontaneous perforation of the esophagus that appears to be the first one in which the rupture occurred in the cervical esophagus. A thirty-five-year-old woman became ill the evening before admission to the hospital complaining of sudden nausea, vomiting and a lump in the throat. A second episode of vomiting produced bright-red blood, and the lump in the throat disappeared. Five hours after onset, swelling of the neck, face and eyes began, and progressive weakness was noted. Previously, the patient had complained of difficulty in swallowing since the age of seventeen. Physical examination disclosed subcutaneous emphysema of the face, neck and upper part of the chest. Physical and x-ray examinations of the chest were negative. A lateral roentgenogram of the neck demonstrated retropharyngeal emphysema. A diagnosis of spontaneous perforation of the esophagus was made, and the cervical esophagus was explored. There was a defect in the anterolateral aspect of the esophagus just before its insertion. The defect was oval and measured approximately 2 by 1 cm. The defect in the mucosa was small. Convalescence was rapid after simple closure of the defect. A postoperative barium swallow demonstrated no abnormalities.

Tuberculosis

Pulver and Michel[135] found 4 cases of esophageal tuberculosis from 1949 to 1953. More esophageal tuberculosis is being reported in elderly patients since it has been recognized that caseous lymph nodes may perforate into the bronchus or the esophagus and so spread the disease. Except for dysphagia or signs of stenosis, symptoms are usually lacking, and there is no

typical radiographic picture to aid in the diagnosis. Most often esophageal tuberculosis is diagnosed at autopsy, after a biopsy to exclude cancer, or when radiation fails to relieve a suspected carcinoma without biopsy confirmation.

Miscellaneous Conditions Affecting the Esophagus

Adams and Luria[136] have reported uncommon benign lesions of the lower esophagus, including hemangioma with a central ulcer and a case of recurrent severe blood loss from a partially thrombosed vessel in a fibrotic lower esophageal plaque, a diaphragmatic hernia, a peptic ulcer in the herniated fundus, a periesophageal granuloma and a huge invasive fundal ulcer.

Curling of the esophagus is discussed by Eskridge and Peake[137] from the clinical and x-ray points of view. The etiology is obscure, and the chief complaint is dysphagia. Pain, when present, is often referred to an area behind the lower half of the sternum, but may vary and can simulate that of gall-bladder, coronary-artery, gastric or duodenal disease. When symptomatic (as in 2 of 15 cases in one series) the condition can be most distressing because of poor therapeutic results. Nineteen cases are presented, and the prediction is made that this condition will be seen more frequently with the aging population.

Schatzki and Gary[138] studied 5 adult males in whom dysphagia was due to diaphragmlike, localized narrowing of the esophagus (lower esophageal ring). The cause of the ring is unknown. Only in extreme cases is surgical intervention required. Education of the patient regarding eating habits relieves the symptoms in most cases.

(To be concluded)

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MEDICAL INTELLIGENCE

MYOTONIA ATROPHICA AND CYANOSIS*

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IN 1909, Steinert described a familial, chronic, slowly progressive disease characterized by visual and glandular disturbances combined with muscular atrophy. This has been called myotonia atrophica, or Steinert's disease, in contradistinction to myotonia congenita, or Thomsen's disease. Recently, a man with Steinert's disease presented, in addition to the usual findings, marked cyanosis. Physiologic studies were done in an attempt to define the cause of the cyanosis.

CASE REPORT

A 57-year-old man was admitted to the hospital complaining of inability to walk for the past 6 years. The illness began at the age of 25, when he noted progressively severe muscular weakness in the lower extremities that soon necessitated the use of a cane. At 29 years of age he became aware of a marked decrease in visual acuity, and at about the same time he became impotent. One year later ability to speak became much impaired because of muscular weakness. Subsequently, he became incontinent of urine, and for 6 years before admission he had been confined to bed because of the muscle weakness.

The family history was significant. His father died of the same disorder, and both a brother and a sister were affected although not as severely as the patient. He had 2 grown sons, but he had lost contact with them and did not know the status of their health.

Physical examination showed a well developed man who appeared chronically ill. He was well oriented and co-operative, but the speech was monotonic, garbled and slurred, giving the impression of subnormal intelligence. The facial expression was flat, and there was bilateral eyelid ptosis. He was completely bald. The temporal muscles were atrophic, and there was striking masseter-muscle weakness. Definite cyanosis of the lips and fingernails was seen.

Visual impairment was severe, probably on the basis of bilateral cataracts. The pupils reacted normally, and the extraocular movements were normal. The palatal arch was high, and there was definite orbicularis oris and tongue weakness. The patient was unable to hold his head erect primarily because of great weakness of the sternocleidomastoid muscle. The chest was symmetrical, and there was a high resting position of the diaphragm, with considerable reduction of motion. The respiratory rate was about 20 per minute, and no rales were heard. Examination of the heart revealed no abnormality except for an unusually prominent pulmonic 2d sound. The abdomen was obese and pendulous, with a weak musculature.

Considerable testicular atrophy was present although the beard and the distribution of pubic hair were normal. The tone of the anal sphincter was poor. Weakness of the arms, forearms, hands, legs and thighs was apparent as well as a bilateral foot drop. No deep tendon reflexes could be demonstrated. Hoffmann's and Babinski's signs were negative, and the abdominal reflexes were present. There was normal sensitivity to testicular and deep tendon pressure.

Routine examination of the urine was negative. The hemoglobin was 20.8 gm. per 100 cc., the red-cell count 6,800,000, and the hematocrit 61 per cent. The total white-cell and differential counts were normal. The total blood volume, with the radioactive-albumin technic, was 7.3 liters. A bone-marrow examination showed only normoblastic hyperplasia. The serum sodium, potassium, phosphorus and calcium and the blood urea nitrogen were normal. A serologic test for syphilis was negative, and the basal metabolic rate was −12 per cent. Liver-function tests were negative.

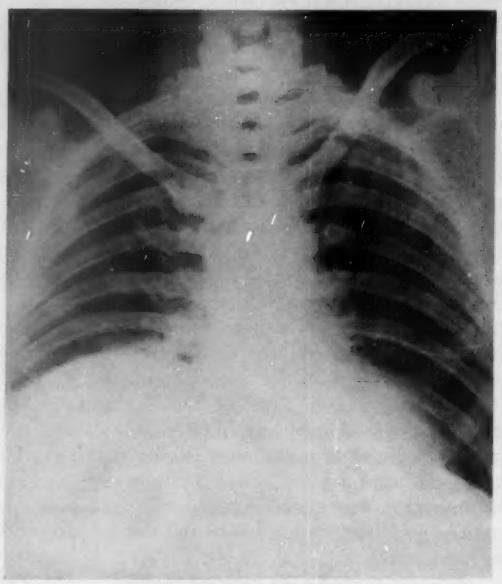

FIGURE 1. *Posteroanterior Film of the Chest, Showing Elevation of the Right Leaf of the Diaphragm, Linear Atelectasis at the Left Base and Mild, Generalized Pulmonary Fibrosis.*

Fluoroscopy of the chest showed linear atelectasis at the base of the left lung in addition to linear areas of fibrosis. The right leaf of the diaphragm was elevated, and movement of the entire diaphragm was restricted (Fig. 1). The heart was not unusual in size or shape. An electrocardiogram was consistent with preponderance of the right ventricle (Fig. 2).

The cardiac-catheterization findings are presented in Table 1, and the studies of pulmonary function are summarized in Table 2.

DISCUSSION

In general the findings in this case fit well with the syndrome of myotonia atrophica. In particular, the diffuse muscle weakness, the familial history, the lenticular opacities and the gonadal dysfunction manifested by hypometabolism and testicular atrophy are characteristic of this disorder.[2]

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Various cardiac abnormalities have been described in myotonia atrophica, including bradycardia, hypotension, and "impure first heart sound."[4] Nonspecific electrocardiographic changes, chiefly conduction disturbances, and arrhythmias have been reported.[5-7] Little reference has been made to the respiratory system, apparently because of a lack of respiratory complaints in these people, but 1 case has been described in which cyanosis was present and the electrocardiogram showed right-bundle-branch block. In addition a diastolic murmur was heard along the left sternal border suggesting that pulmonary hypertension was present.[5]

Before the studies of pulmonary function in the case reported above, it was thought that the oxygen desaturation was probably extracardiac and related chiefly to the great muscle weakness in the thorax and diaphragm, resulting in simply a pulmonary ventilatory defect. The reduction in total lung volume, the high alveolar nitrogen concentration after the breathing of 100 per cent oxygen, the high carbon dioxide pressure and the arterial oxygen desaturation all fit well with the hypothesis of impaired alveolar ventilation. The high functional residual air resembles the usual finding in severe pulmonary emphysema, in which one of the abnormalities is also impaired alveolar ventilation. The arterial oxygen desaturation could also be explained by possible "shunting" of blood directly from pulmonary arteriole to pulmonary venule in areas of lung that were improperly ventilated, as demonstrated in other conditions. The fact that the arterial oxygen saturation rose to only 86 per cent after breathing of 100 per cent oxygen is evidence that this shunting mechanism accounted in part for the cyanosis. The presence of areas of linear atelecta-

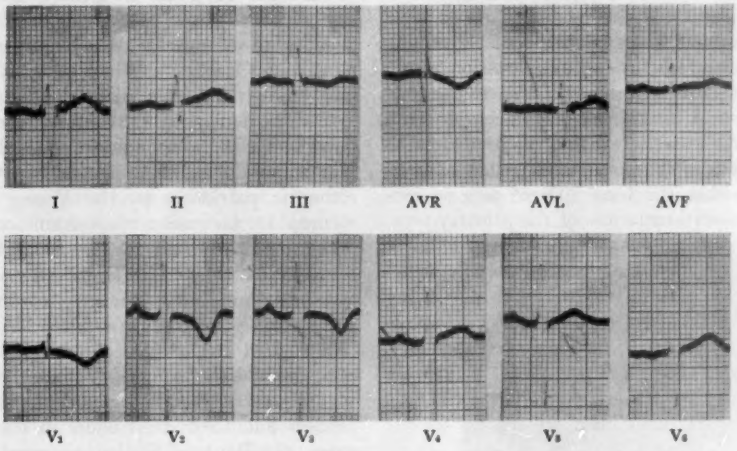

FIGURE 2. *Electrocardiogram, Interpreted As Showing Sinus Rhythm and Right-Axis Deviation.*

TABLE 1. *Cardiac-Catheterization Data in a Case of Myotonia Atrophica.*

VESSEL	PRESSURE	SATURATION
	mm. Hg.	%
Pulmonary artery	31 (mean)	51
Right ventricle	37/9	
Right atrium	7 (mean)	
Femoral artery		72
Femoral artery after 6 min. of 100% oxygen		86

TABLE 2. *Pulmonary Function in a Patient with Myotonia Atrophica and in a Normal Person.*

SUBJECT	COMPLEMENTAL AIR	TIDAL AIR	RESERVE AIR	RESIDUAL AIR	ALVEOLAR NITROGEN	FUNCTIONAL RESIDUAL AIR	TOTAL LUNG VOLUME	RATIO OF FUNCTIONAL RESIDUAL AIR TO TOTAL LUNG VOLUME	MINUTE VOLUME	ALVEOLAR VENTILATION	ARTERIAL pH	ARTERIAL CARBON DIOXIDE PRESSURE	VITAL CAPACITY
	cc.	*cc.*	*cc.*	*cc.*	%	*cc.*	*cc.*	%	*liters/ min./ sq. meter*	*liters/ min./ sq. meter*		*mm. Hg.*	*cc.*
Patient	440	280	60	600	6.1	662	1102	60	2.85	1.33	7.4	56	500
Normal person*	3000 (2900-3300)	500	950 (849-1060)	1325 (1200-1400)	2.5	2275 (2000-2500)	5310 (4300-6700)	25-36	3.60	2.20	7.35-7.45	40-45	3600

*Values based on data of Robinson[1] & Comroe.[2]

sis in the lung makes such an explanation even more likely. However, the other values suggest that the major factor in the cyanosis was impaired alveolar ventilation based on the muscular abnormality present in myotonia atrophica.

The mean pulmonary-artery pressure of 38 mm. of mercury represents at least a twofold elevation above the normal value. It is quite comparable to the pulmonary hypertension found in severe emphysema and in severe kyphoscoliosis. The polycythemia is likewise a compensatory response to impaired oxygenation of blood within the lung. There was no evidence that the polycythemia was of the primary type.

In essence, the marked cyanosis in this case of myotonia atrophica appears to have been related to weakness of thoracic and diaphragmatic muscles, resulting in impaired alveolar ventilation and incomplete oxygen saturation of blood in the pulmonary capillary. An additional factor of shunting from pulmonary arteriole directly to pulmonary venule in atelectatic areas of lung may also have been present.

Summary

A case of myotonia atrophica with cyanosis and polycythemia is presented. The major factors in the production of the cyanosis seem to have been impaired alveolar ventilation possibly combined with arteriovenous shunting in areas of atelectasis in the lung.

Moderate pulmonary hypertension was also present.

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DOCTORS AFIELD

General Hugh Mercer

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AMONG the many physicians who won fame in fields other than medicine, those who relinquished their medical careers to serve as soldiers in the armies of their country deserve special recognition. These men frequently unite the qualities of the fearless warrior with those of the gentle man of learning, and no one more nobly illustrates this combination of the medical and the martial temper than General Hugh Mercer.

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On April 16, 1746, an army of kilted Highlanders marched into battle at Culloden in Scotland, singing jauntily, to the tune of their bagpipes, "Wha shall be King but Charlie?" When Charles Edward Stuart had landed in Scotland, he found an impoverished and dispirited people, painfully conscious of being governed from London and exploited by the English. The sullen discontent, however, was transformed into romantic patriotism by the Young Pretender, who seemed to promise a new dominion for oppressed Scotland if his dash for the English throne should meet with success. The Highland clans flocked to his standard, and Hugh Mercer, a young doctor from Aberdeen, who had graduated from the medical school of Marischal College less than two years previously, joined the army of "Bonnie Prince Charlie" as an assistant surgeon. Despite the heroism of the Highlanders and their deep belief in the justice of their cause, the Battle of Culloden turned into a complete victory for the English, and here the final doom of the house of Stuart was sealed. The remnants of the defeated army were remorselessly pursued by the English, who were bent on the complete destruction of the clan system and the thorough subjugation of the rebellious Highlanders. Among the survivors of the battle who sought safety from English persecution in flight to foreign lands was Dr. Hugh Mercer, who embarked for America in the autumn of 1746, being then twenty-one years old.

Mercer landed in Philadelphia, but he soon migrated to a settlement on the western border of Pennsylvania that was then at the edge of the wilderness. He is credited with planning the town that grew out of this settlement and that now bears the name Mercersburg.[1]

In America Mercer continued to practice medicine and led a busy and perilous life on the frontier of civilization, functioning not only as a physician but also as a surgeon and an apothecary. He, like other doctors who practiced along the sparsely settled western frontier, was obliged to travel great distances through wild forests, under the constant menace of attack by marauding Indians. Day after day Dr. Mercer rode out on his visits to the sick — his saddlebags filled with medicines and with the inevitable lancets for bloodletting.

At the outbreak of the French and Indian War, Mercer enlisted for duty not in the medical service but in the line. He was appointed captain in the army of General Braddock and was wounded during the disastrous defeat at Fort Duquesne in 1755. He then returned to his old locality and to the practice of medicine, but the defeat of Braddock had exposed all of western Pennsylvania to the depredations of the Indians, and life in the frontier settlements became increasingly precarious. To meet this menace, the set-

tlers formed military associations for their self-protection, and Mercer left his local practice again to serve at Fort McDowell as physician and surgeon to the garrison as well as captain of infantry. In the following year he was given command of all forces in the province of Pennsylvania west of the Susquehanna. He took part in General Forbes's successful expedition against Fort Duquesne in 1758, and his troops formed part of the command of Colonel George Washington. The captured fort was rechristened Fort Pitt and provided with a garrison of 200 men under the command of Hugh Mercer, who thus became the first man in official authority at the very beginning of the city of Pittsburgh.[2] Whether or not he also practiced medicine there is subject to conjecture.

Shortly after Mercer was relieved of his command of Fort Pitt in 1760, he moved to Fredericksburg in Virginia. He probably did this on the advice of George Washington, with whom he had begun an intimate and lasting friendship during the Forbes expedition. In Fredericksburg he married and soon became the leading physician of the town. His massive prescription and accounting book for this period has been preserved and constitutes an important record of medical and pharmaceutical practice in the Colonies.[3] From this record it is known that Dr. Mercer treated Mary Ball Washington, George Washington's mother, and visited her eleven times. The nature of her illness is not indicated, but the treatment consisted of bleeding, blistering, purging and the administration of emetics. James Madison consulted Dr. Mercer and paid him for a purge and a mixture for dispelling fever. George Washington himself was treated by Mercer, as well as many members of his family. Mercer attempted the treatment of Martha Parke Custis, the daughter of Martha Washington by her first marriage, who suffered from epilepsy, but he failed to bring about any improvement in the child's condition, much to the disappointment of George and Martha.[4]

Aside from his medical work Mercer took a keen interest in the momentous political issues of the day. His apothecary shop became a rendezvous for many of the leaders of American thought and action. Washington kept there a personal desk where he transacted business whenever he was in Fredericksburg.[5] Into this shop came James Monroe and George Weedon, and probably also John Paul Jones and John Marshall and George Mason, to discuss the latest British invasion of the liberties of the Colonies and to consider measures of resistance against the encroaching tyranny.

Mercer's announcement to the Virginia House of Burgesses, after the battles of Lexington and Concord, declaring his willingness to serve in the militia is characteristic of his selfless spirit of patriotism. Instead of making a request for an exalted commission, he simply wrote, "Hugh Mercer will serve his adopted country and the cause of liberty in any rank or station to which he may be appointed."[6] He was given the rank of colonel and the command of the Third Virginia Regiment. At the head of his men he marched away from Fredericksburg — never to return.

During the early part of 1776 Mercer was in Williamsburg, where he was entrusted with the formidable task of training and disciplining the raw and often mutineering mob that represented the Army of Virginia. On June 5, 1776, he received from Congress the commission of brigadier general — probably at the instance of Washington himself — and was ordered to join the Commander-in-Chief in New York. Mercer accompanied Washington during his retreat across New Jersey in the latter part of 1776—

General Hugh Mercer (Reproduced from Woodhouse[7] with the Permission of the Publishers).

a retreat that only ended when the Americans encamped on the Pennsylvania side of the Delaware and placed between themselves and the foe a broad and rapid river filled with ice.

On the memorable Christmas night of 1776 General Mercer crossed the perilous Delaware with Washington and played a prominent part in the brilliant American attack on the Hessians at Trenton. His column operated on one of the main routes of escape from the startled town and, by obstructing the retreat of the enemy, enabled the Americans to capture 1000 prisoners, along with valuable stores of ammunition and provisions.

Despite this victory the Americans found themselves in a desperate position several days later. Cornwallis had hurried toward Trenton with 5000 veteran British troops to halt the advance of the Continental Army. The fate of the struggling colonies seemed to hang tremblingly in the balance on the night of January 2, 1777, and General Mercer's headquarters was the scene of an anxious council of war. The overwhelming force of the enemy made an open battle inadvisable, and the almost impassable Delaware closed the avenue of retreat. It was General Mercer, accord-

ing to some historians, who suggested the magnificent alternative of passing around the left flank of the enemy under cover of darkness and attacking, on the following morning, the British detachment that had been left at Princeton. The evidence that Mercer was the author of this plan is inconclusive, but more certain is the fact that he favored offensive enterprise, rather than cautious retreat, as the proper American military policy and supported proposals for forthright and decisive action.

Washington set out for Princeton with his ragged troops shortly after midnight, leaving his watchfires burning brightly to deceive Cornwallis, who was resting for the night, secure in the belief that the Continental Army was trapped and would easily be captured in the morning. After dawn on January 3, as the American army was approaching Princeton, Washington sent General Mercer, with a detachment of about 400 men, to seize a bridge over Stony Brook. Colonel Mawhood, the British commander at Princeton, had just crossed the bridge and was marching with his forces toward Trenton when he spied Mercer's troops on their way to the bridge, unaware of his presence. Mawhood hurried back across the bridge and led his men in a dash for an orchard, which was situated on a piece of rising ground. But the Americans reached the orchard first and formed behind a fence, facing the British, who were deployed in an open field below. After three volleys were exchanged, the British charged with bayonets, and the Colonists were driven back in disorder. General Mercer's horse had been shot from under him, and, as the British overran the American position, he tried vainly to rally his broken troops on foot. Finally he was brought to the ground by a blow from the butt of a musket, and the British troopers who surrounded him demanded that he surrender. Instead of asking for quarter, the doughty Scottish doctor lunged with his sword at the nearest man. He was then bayoneted on the ground and left lying on the field.

At this point Washington swung his reinforcements into position, exposing himself to the hottest fire of battle, and turned the day into a thrilling victory for the Americans. But Washington, describing the Battle of Princeton in his official report to Congress, says, "This piece of good fortune is counterbalanced by the loss of the brave and worthy General Mercer."[7] The Battle of Princeton provided a triumph that infused a spirit of hope and a will to win into the languishing cause of the Colonies, but as news of the victory was spreading abroad, Hugh Mercer died in a Princeton farmhouse on January 12, with Dr. Benjamin Rush at his bedside. His mangled body was removed under military escort to Philadelphia, where it was exposed to the public for a day to excite, by so mournful a spectacle, the indignation of the people. The hero's remains were then buried with military honors in Philadelphia.

Hugh Mercer has received due recognition for his gallantry on the battlefield, and counties in several states bear his name, including the county in New Jersey where Princeton and Trenton are situated. But Mercer also deserves to be remembered as a military man who combined gentler virtues with his martial ardor and as a respected physician and a man of learning who was always ready to assume the gravest duties of community citizenship and to champion the aspirations of the people among whom he was living. In the words of an English traveler — a man unfriendly to the American cause — who met Hugh Mercer in Fredericksburg: "Dr. Mercer was generally of a just and moderate way of thinking and possessed of liberal sentiments and a generosity of principle very uncommon among those with whom he had embarked."[8]

The finest tribute to General Mercer's character as a bold warrior and a cultivated physician appears in an inscription on the monument that stands near his grave in the Laurel Hill Cemetery in Philadelphia. The inscription reads: "General Mercer, Physician, Fredericksburg, Virginia. Distinguished for his skill and learning, his gentleness and decision, his refinement and humanity. . . ."[2]

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 41181

PRESENTATION OF CASE

A fifty-eight-year-old man was admitted to the hospital because of chest pain of three and a half hours' duration.

The patient went to bed early feeling well the evening before admission. At 1:30 a.m. he awoke clearing his throat and coughing. Shortly thereafter, he had a severe, crushing substernal pain that radiated to both arms and was followed by several bouts of vomiting, pallor and collapse. When he was seen by a physician an hour and a half after the onset of the pain, he was still in pain and was vomiting; 15 mg. of morphine sulfate was administered, without relief. Thirty or forty-five minutes later another dose was given, with only slight relief.

He had been an active, hard-working person all his life. He was said to have had moderate hypertension for a number of years; however, this was asymptomatic, and he had received no therapy for it. For the past several months he had had cough and expectoration of a considerable amount of mucus. There was no history of chest pain or other serious illnesses.

Physical examination revealed a slightly obese man who was pale, cold and sweaty. He was vomiting and complaining of chest pain. Examination of the head was negative. The neck veins were flat. The trachea was in the midline. The lungs were normal. The left border of the heart was 1 cm. to the left of the midclavicular line. There were no murmurs, friction rub or gallop rhythm. The abdomen was normal except for some tenderness in the epigastrium. There was no edema or cyanosis of the extremities. The pulses were not palpable in the feet. The deep tendon reflexes were present and equal bilaterally.

The temperature was 97.5°F., the pulse 60, with premature beats every three or four beats, and the respirations 20 and shallow. The blood pressure was 200 systolic, 130 diastolic.

The hemoglobin was 16.3 gm. per 100 cc.; the white-cell count was 17,800, with 93 per cent neutrophils. An electrocardiogram showed a normal sinus rhythm at a rate of 85. There were frequent ventricular ectopic beats. The PR interval was 0.18 second, and the QRS interval 0.08 second. The ST segment was elevated in Leads 1 and aVL. The R waves were absent and the ST segment elevated in Leads V_2, V_3 and V_4. There was a small Q wave and an elevated ST segment in Lead V_5.

The patient was put on strict bed rest and was given 0.15 gm. of quinidine lactate and 100 mg. of Demerol intramuscularly and 8 mg. of morphine subcutaneously. Within the next six hours 120 mg. of Sodium Luminal and an additional 10 mg. of morphine sulfate were administered. Five hours after admission his condition appeared to be stabilized, with a pulse of 80, a blood pressure of 180 systolic, 120 diastolic, and a respiratory rate of 20. He was essentially without pain and was sleeping intermittently. There were no signs of cardiac decompensation. Two hours later he complained of a recurrence of chest pain, which within five minutes became intolerable. The nurse left to obtain medication and on her return found him markedly cyanotic. He had some convulsive movements, drew several agonizing breaths and died ten and a half hours after the onset of his illness.

DIFFERENTIAL DIAGNOSIS

DR. HOWARD B. SPRAGUE*: A few days ago Dr. Castleman remarked to me that because of the improvements in diagnostic procedures and clinical acumen over the past several years he has had difficulty in selecting cases that presented any diagnostic challenge. Therefore, when I read this history, I thought to myself: What is the "catch" in this apparently straightforward description of coronary-artery disease? Certainly, this man must have had an acute coronary thrombosis. When I looked at the electrocardiograms they seemed to be conclusive of myocardial infarction of the anteroseptal type with transmural destruction. As Dr. Castleman knows, I have been reviewing the cardiac cases presented at the clinicopathological conferences in this hospital, and I am in the stage when I believe that anything can happen, or if it has not happened that it will happen sometime.

I call attention to one statement in the protocol that I assume is put in to bring some doubt to my mind — namely, that the pulses were not felt in the feet. This brings up the possibility of dissecting aneurysm or of coarctation of the aorta as a background for the hypertension. I am willing to believe that the reason the pulses were not felt was that the examination was made during the severe vasoconstriction of the acute episode and that these diagnostic possibilities are unlikely. I came to the conclusion, then, that what I

*Physician, Massachusetts General Hospital.

am expected to determine is the exact nature of this man's death.

During an acute coronary occlusion with myocardial infarction the patient may die suddenly from one of several causes — extension of the infarction, massive pulmonary embolism, cardiac arrest, ventricular fibrillation or cardiac rupture. As a matter of coincidence, last week I finally got around to reading in the *Boston Medical and Surgical Journal* of 1880 a case report of cardiac rupture by Winsor.[1] That case is considered by some authors the first one in which a clear connection between coronary thrombosis, myocardial infarction and cardiac rupture was drawn, under the title of "Angina Pectoris, with Rupture of the Heart." The patient lived for four days after the onset of severe pain. The meticulous way in which the timing of the death in the case under discussion is given perhaps holds a certain hazard in relation to a diagnosis of ventricular rupture — the patient died ten and a half hours after the pain began. Usually, ruptures occur in two to seven days.

Before going on, I have one other statement to make. The sporting nature of these exercises depends on the discusser's having no foreknowledge of the case to be presented. Two or three days ago, when I was on a "visit" with my house staff, one house officer said to the other, "I understand that a patient came in with myocardial infarction and turned out to have myocardial rupture." When I read this protocol I was in a quandary, wondering whether I ought to turn it back to Dr. Castleman. I had no way of knowing whether this was the case of cardiac rupture or not. If I declined the discussion, and it turned out not to be this case, I should be embarrassed. I concluded finally that from the standpoint of a teaching exercise I should defend the diagnosis of ventricular rupture, for it seemed to me that the patient had to a nearly perfect degree the combination of circumstances making that diagnosis really tenable. I have paid what I trust is unnecessary deference to my integrity, and come here with clean hands. If I go down, I shall go down with pleasure.

What are the elements that made this patient liable to ventricular rupture? He was a male over fifty years of age who died in the first three days of his illness. Although it seems likely that more females than males have ruptures after myocardial infarction, the figures indicate that more males have them in the first three days. Secondly, there was no previous history of angina, but there was one of hypertension. Thirdly, — and this is striking, — severe hypertension persisted during a severe myocardial infarction and for some hours afterward. I noted in the report by Edmondson and Hoxie[2] about the relation of hypertension to myocardial rupture these words: "rupture often followed the first attack of coronary thrombosis in persons who had hypertension and some degree of cardiac hypertrophy, and whose hypertension persisted after infarction." This observation has been made by others including Mallory, White and Salcedo-Salgar.[3] Fourthly, there was severe localized myocardial necrosis in the anterior wall of the left ventricle near the septum, with apparently good heart muscle elsewhere. The patient also had a moderately high white-cell count, — almost 18,000, — and he died with a recurrence of unbearable pain. It seems to me that neither extension of infarction, pulmonary embolus nor the abrupt death from arrhythmia would be associated with pain that in five minutes became unbearable and was followed by cyanosis and sudden death.

Ten and a half hours is a shorter time after the onset of acute coronary occlusion than I myself have seen in cardiac rupture, but I do not believe it is unique. In the cases of acute myocardial infarction described by Friedman and White[4] 10 out of 105 ruptured; of those, 2 ruptured in twelve hours, and 1 in fourteen hours. The group in Griffith's clinic[5] reported 1026 cases of fresh infarcts, with a percentage of rupture of 7.1; of these patients 17.5 per cent died less than twenty-four hours after onset. The article states that in some cases the patients died within a few hours, at a time when there was not an opportunity to have a good work-up. I do not know what the shortest time is in which the heart can rupture after a myocardial infarct. The report from Griffith's clinic and other reports in the literature have implied that ruptures are rare under the age of fifty and that unlimited activity tends to increase their frequency. The series of Beresford and Earl[6] and of Jetter and White[7] have shown that patients in mental institutions who could not be properly restricted after myocardial infarction had a much higher rate of cardiac rupture.

Rupture occurs in the first few weeks, is rare in old scars, is three times as common in patients whose hypertension persists after the occlusion and is four times as common if the coronary circulation was previously adequate. This man had no history of angina pectoris; his illness occurred out of a clear sky, and acute myocardial necrosis must have been present. One can carry this even farther and use the observations that Wessler, Zoll and Schlesinger[8] made on the pathological substrate, as they called it, of myocardial rupture. They said "that the findings characteristic of ruptured hearts were: fresh coronary occlusion; recent myocardial infarction transmural in extent in an area poorly supplied with collateral vessels, and in which fibrosis was entirely absent at least in one area." We can draw a parallel in this case.

It has been remarked[2] that hearts that rupture tend to be smaller and lighter than those that do not rupture. The patient with a large heart and low blood pressure goes into congestive heart failure; the person with high blood pressure and a relatively small heart may have a rupture, even through a small infarct, for a well functioning major portion of the left ventricle is pumping against a small, weak area. I shall ask if this patient's heart weighed 458 gm., which is the average weight of those that rupture, as contrasted

with a weight of 488 gm. There is also some question whether there is an increase in the subepicardial fat in such persons. It has even been suggested that in some patients there is a large collection of leukocytes in the reactive region of the infarct and that the destruction of the polymorphonuclear leukocytes liberates a proteolytic enzyme, which may be a factor in myocardial dissolution.

I have been quite dogmatic. Perhaps this patient did not have a coronary occlusion at all. However, I am going to say that he had acute thrombosis of the left anterior descending coronary artery, with myocardial infarction involving the anterior region of the left ventricle adjacent to the septum; that he probably had a patent right coronary and perhaps a patent left circumflex artery, with relatively normal muscle in the posterior and lateral areas; and that the anterior wall of the left ventricle ruptured presumably by a dissecting type of process rather than through a straight "blow out." I rest my case.

DR. ROBERT E. SCULLY: Dr. Butterworth, should you like to comment?

DR. J. SCOTT BUTTERWORTH*: I am reminded of a case that was presented here a long time ago by Dr. Soma Weiss in which I learned all I know about one of the possibilities that Dr. Sprague mentioned. I am sure he is entirely right, but, if I were discussing this case, I should be inclined to take one of the other possibilities as my first choice. I think I should favor a dissecting aneurysm of the aorta, descending into the coronary arteries and producing myocardial infarction.

DR. RICHARD J. CLARK: I should like to ask Dr. Sprague some questions. Are you disturbed by the high white-cell count within several hours? Would you entertain the possibility that this patient had an infarction dating back a number of days? The reason that I ask this is that I have recently seen a patient with an almost identical story, who came into the hospital with excruciating pain and died forty-eight hours later with a ruptured myocardium. He had a small heart and high blood pressure. The interesting point is that after microscopical examination the pathologist stated that the infarction was at least eight days old, although the patient had had no symptoms at all during the previous four or five days. This situation is extremely interesting to us in view of the workmen's compensation cases in which the time relation of exertion to onset of symptoms assumes real importance.

DR. SPRAGUE: I have no way of suspecting that the patient under discussion had a myocardial infarction of that duration. He merely went to bed that night feeling as well as ever; he never had any angina. I think that this was probably an unusual case. The white-cell count, I think, is compatible with my diagnoses.

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CLINICAL DIAGNOSIS

Recent anterior myocardial infarction.

DR. HOWARD B. SPRAGUE'S DIAGNOSES

Thrombosis, left anterior descending coronary artery.

Myocardial infarction anterior left ventricle, with rupture.

ANATOMICAL DIAGNOSES

Acute myocardial infarct (ten and one half hours), anterior left ventricle, with rupture and hemopericardium.

Coronary thrombosis, recent, anterior descending branch of left coronary artery.

Cardiac hypertrophy, hypertensive type, slight.

PATHOLOGICAL DISCUSSION

DR. SCULLY: Dr. Sprague was almost entirely right in his prediction of the pathological findings in this case. The only mistake he made was in the weight of the heart. This was 435 instead of 458 gm.

When the thorax was opened the pericardial cavity was seen to be distended with half a liter of blood. On the anterior aspect of the left ventricle adjacent to the septum was an L-shaped area of hemorrhage into the epicardium measuring 5 by 2 cm. There were four ragged tears, varying from 0.5 to 1.5 cm., through the underlying myocardium. The myocardium surrounding the hemorrhagic zone was slightly boggy. The hemorrhage extended for a short distance into the interventricular septum. There was a fresh occlusion in the anterior descending branch of the left coronary artery 3 cm. from its origin. The right coronary and the circumflex branch of the left coronary artery showed no occlusions, so that this episode must have been the first. Microscopically, the thrombus overlay a large atheromatous plaque (Fig. 1). In the center of the thrombus there were cholesterol crystals and histiocytes laden with fat (Fig. 2). In other words an atherosclerotic plaque must have ruptured, with secondary thrombosis in relation to its contents. The infarct microscopically was transmural. There was a very fresh thrombus on the endocardial surface. The fibers of the infarcted muscle were shrunken and had a smudgy appearance, and their nuclei showed pyknosis. There was a fair amount of neutrophilic infiltration, which was confined to the subendocardial myocardium. This localization is unusual because typically this region is the slowest to react to an infarct. We believe that the microscopical findings are consistent with ten and a half hours' duration. There were no other significant findings except for slight arteriolar changes in the kidneys, which would go along with the hypertension.

DR. SPRAGUE: The question raised by Dr. Clark is worthy of further comment. It illustrates the diffi-

culty in determining the age of myocardial infarcts and injects doubt concerning the time of onset of

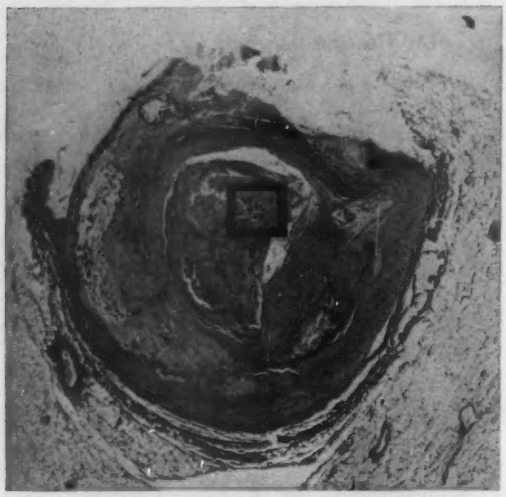

FIGURE 1. *Fresh Thrombus Overlying the Atherosclerotic Plaque.*

coronary occlusion. It is evident that some areas of a slowly occluding thrombus in a vessel may present

FIGURE 2. *High-Power View of the Area Blocked off in Figure 1.*
Note cholesterol clefts within the thrombus.

microscopical signs of organization and may be much older than the final, totally occluding, plug. It is also true that a myocardial infarction may be slow in onset and even painless, or may be found as a surprise at autopsy as a final event in moribund or obtunded patients. However, I consider it unjustified to assume that an abrupt, total occlusion of a coronary vessel, especially a large one, with transmural myocardial infarction, can result in any clinical response except that typical of acute interference with coronary supply — pain, collapse, leukocytosis and the diagnostic electrocardiogram. The nocturnal onset of the attack in the case just discussed must have coincided with the complete occlusion, when the atheromatous material blocked the vessel. Much has been written about the relation of effort to the mechanisms of coronary occlusion caused either by subintimal hemorrhage in a coronary vessel or by rupture of an atheromatous ulcer in such a vessel and embolism of plaque contents to smaller radicles. This case illustrates, to an unusually clear degree, the latter process and demonstrates its fortuitous character since it occurred when the patient was quietly asleep in bed.

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CASE 41182

PRESENTATION OF CASE

A seventy-four-year-old Negro entered the hospital because of progressive exertional dyspnea and weakness.

Until two years before admission he was in good health; then he began to have frequent colds, which lasted longer than usual. He was, however, able to work as a laborer, laying railroad ties, until eight months before admission, when he had an illness diagnosed as viral pneumonia that was characterized by low-grade fever, cough productive of a moderate amount of white sputum and some dyspnea. He was confined to bed for two months. Since that time he had had increasing dyspnea on exertion and weakness to the point that he stayed in bed most of the time. He became increasingly anorectic and lost 25 pounds. Three months before admission a painful lump suddenly developed in the left chest wall that grew rapidly but became painless. Two or three

weeks before admission an x-ray film of the chest showed "a shadow," and his physician referred him to the hospital.

He was an occasional cigarette smoker (one or two packages a week). He had been well except for gonorrhea and primary and secondary syphilis treated with a few injections, during middle age. His physician had been treating him for "heart trouble" for a year; he had had intermittent slight ankle swelling, as well as orthopnea requiring two pillows for relief, during the several months before admission. For several years he had had nocturia, frequency, a feeling of urinary retention and a decreased force of the urinary stream.

Physical examination revealed a chronically ill, extremely weak, dyspneic man. The pupils reacted to light and on accommodation. The trachea appeared deviated to the right to some observers. There was dullness, with absent beats, at the left lung base to the tip of the scapula, and decreased breath sounds to the angle of the scapula. A firm, irregular mass, 10 by 6 cm., was attached to the sixth rib in the left anterior axillary line. The point of maximal impulse of the heart was 9 cm. lateral to the midsternal line; there was a Grade 2 aortic systolic but no diastolic murmur.

FIGURE 1. *Posteroanterior Roentgenogram of the Chest after Thoracentesis, Showing Residual Fluid at the Left Base. The heart exhibits prominence of the left ventricle; there is some engorgement of the pulmonary vessels.*

The aortic second sound was much louder than the pulmonic. The liver edge was palpable 1 fingerbreadth below the right costal margin. The extremities were normal. A "Parkinsonian-like" tremor of the hands with an intention tremor was present.

The temperature was 100.2°F., the pulse 120, and the respirations 24. The blood pressure was 180 systolic, 90 diastolic.

Urinalysis showed a specific gravity of 1.010, a ++++ test for albumin and 50 to 60 white cells, many in large clumps, per high-power field in the sediment. A urine culture grew a few coliform and a few *Staphylococcus albus* organisms. A test for Bence-Jones protein in the urine was negative on two occasions. A phenolsulfonphthalein test revealed 15 per cent excretion of dye in four hours. Examination of

FIGURE 2. *Spot Film of the Left Fifth Rib, Showing Extensive Destruction of its External Portion Associated with a Large Soft-Tissue Mass.*

the blood disclosed a hemoglobin of 5.2 gm. per 100 cc., a hematocrit of 17 per cent and a red-cell count of 1,750,000. Wintrobe indexes were mean corpuscular volume 99 cubic microns (normal, 80-94 cubic microns), mean corpuscular hemoglobin 32 micromicrogm. (normal, 27-32 micromicrogm.) and mean corpuscular hemoglobin concentration 34 per cent (normal, 33-38 per cent). The white-cell count was 4600, with 61 per cent neutrophils, 29 per cent lymphocytes, 9 per cent monocytes and 1 per cent basophils. A reticulocyte count was 0.8 per cent. The fasting blood sugar was 93 mg., the nonprotein nitrogen 38 mg., the total protein 7.0 gm., the albumin 4.5 gm., the globulin 2.5 gm. and the alkaline phosphatase 1.9 units per 100 cc. A stool guaiac test was negative. An electrocardiogram showed ST-segment changes suggestive of hypertrophy of the left ventricle or coronary-artery disease or both. An x-ray film of the chest demonstrated a left-sided pleural effusion, with displacement of the mediastinum to the right, and a destructive lesion involving the left fifth rib (Fig. 1 and 2).

The patient received digitalis and supportive therapy. A left-sided thoracentesis was performed two days after admission, with the removal of 800 cc.

of serosanguineous fluid. The protein content of this fluid was 5.3 gm. per 100 cc., and it contained 45,000 red cells and 1700 white cells per cubic millimeter. A cell block of this fluid was reported as showing no malignant cells. He was given 1000 cc. of whole blood, which raised the hemoglobin to 7.6 gm. per 100 cc. On the fifth hospital day a biopsy of the rib mass was performed.

Differential Diagnosis

Dr. William H. Baker*: This case resolves itself into a differential diagnosis of a mass in the left anterior portion of the chest associated with severe systemic symptoms, loss of weight, anorexia, kidney disease and severe anemia. When I first read this protocol I thought immediately of multiple myeloma because that seemed best to explain the symptoms, the signs of renal failure, the anemia and the osteolytic lesion with a mass presenting anterior to it in the left rib.

There are other conditions that I should consider, however. Mycotic infections, which are rare, to be sure, can certainly produce this picture, but usually without the anemia. Actinomycosis commonly involves the rib but usually presents as an abscess, with multiple sinuses leading to the outside and the presence of sulfur granules in the drainage. The other mycotic infections such as blastomycosis, torulosis and coccidioidomycosis can produce this picture but rarely involve the rib; also, they are associated with other manifestations of disease that were not present in this patient. Tuberculosis must be considered, especially in a Negro, but tuberculosis usually involves the joint surface and rarely the diaphysis of bone. Boeck's sarcoid should be considered in a Negro, but it ordinarily involves the terminal phalanges and usually does not involve the rib.

Another strong consideration here, of course, is syphilis, for the patient had had primary and secondary syphilis, treated, I suppose, by injections of heavy metals. (The infection occurred before the discovery of penicillin.) Tertiary syphilis, with its periostitis and osteolytic lesions that sometimes cannot be distinguished from neoplastic bone disease, together with a gumma, certainly would explain the picture, but it would not explain the kidney disease, as evidenced by the ++++ test for albumin, the phenosulfonphthalein test and the inability to concentrate the urine above 1.010.

I do not think I need consider the benign tumors, for the course was malignant. The patient lost weight, had anorexia and had severe anemia. Benign tumors rarely cause these constitutional symptoms; moreover, benign tumors of bone in this age group are rare. Benign giant-cell tumor could have produced the x-ray picture as it was described, but it rarely occurs in the rib, especially at this age. Monostotic fibrous dysplasia does not need to be considered because it involves primarily the rib itself and does not produce external masses. Therefore, I think I must consider malignant tumors involving the bone. At this point I should like to see the x-ray films.

Dr. Joseph Hanelin: The films of the chest taken on admission show a fairly sizable effusion in the left side of the thorax obscuring about half the lung field (Fig. 1). The heart, after the fluid has been removed, is shown to be enlarged, primarily in the region of the left ventricle. The aorta is tortuous, the pulmonary vessels are moderately engorged, and there may be some congestive heart failure. The mass is extremely hard to see, as is the rib destruction in the conventional films, although excellent spot films taken at the time of fluoroscopy show extensive destruction of the left fifth rib in its anterior axillary portion; the destruction of bone is virtually complete although a few small fragments of bone remain (Fig. 2). I do not see anything in the lungs to account for the effusion. The effusion itself may have been secondary to the rib lesion, which must be a malignant tumor of some sort.

Dr. Baker: Do you see any lesions elsewhere?

Dr. Hanelin: No; I am unable to see any other lesions in the bones. The soft-tissue density across the trachea at the level of the thoracic inlet, I think, can be explained by vessels in that area rather than by an enlarged thyroid gland.

Dr. Baker: This tumor involving the rib was primarily osteolytic, with very little osteoblastic reaction, which is an important point in the consideration of tumors of the bone. No other tumors were present in the remainder of the bones. I was hoping to see other osteolytic areas to strengthen my diagnosis of multiple myeloma.

There is another fact that I should like to know. Was a rectal examination done?

Dr. Richard B. Cohen: The rectal examination showed a prostate enlarged two or three times the normal size and nothing else of significance.

Dr. Baker: This man had symptoms of prostatic obstruction — increasing urgency, frequency and decreased force of the urinary stream. That no nodules were found on palpation of the posterior lobe is some evidence against a prostatic carcinoma.

Was an acid phosphatase determination done?

Dr. Cohen: No.

Dr. Baker: That may be elevated, with only a solitary metastatic lesion from the prostate. The absence of osteoblastic reaction makes carcinoma of the prostate highly unlikely, although carcinoma of the prostate sometimes produces osteolytic lesions. The common primary tumors that spread to bone are from breast, kidney, lung, thyroid gland and prostate. There is no clinical evidence of a primary tumor of the male breast that produces an osteoblastic and osteolytic reaction. The neoplasms that commonly cause an osteolytic type of reaction are tumors from the lungs, kidney and thyroid gland. Classic hypernephroma is often unassociated with renal symptoms,

*Assistant in medicine, Massachusetts General Hospital.

the first indication of hypernephroma being a metastasis either in the rib or in some other bone. Hypernephroma would explain most of the picture as well as the anemia. The absence of previous hematuria and of flank pain and the tubular impairment, as evidenced by the very poor phenolsulfonphthalein excretion, are not explained by a hypernephroma. Hypernephroma usually involves only one kidney, and the phenolsulfonphthalein excretion is usually normal. There was no good clinical evidence of a primary tumor in the thyroid gland or in the lung.

Ewing's tumor could present this picture; this is usually a tumor of persons under twenty years of age. Primary reticulum-cell sarcoma of bone occurs after the age of twenty-five, but I do not think this was a primary reticulum-cell sarcoma. The absence of lymph nodes and a truly enlarged liver and spleen tend to rule out Hodgkin's disease[1] or other types of lymphoma. The lymphomas can produce this picture: the osteolytic destructive lesion with a mass presenting in the chest, the anemia and the renal changes. So many diseases can result in this whole set of symptoms that it is difficult to make one diagnosis.

I shall try to defend my diagnosis of multiple myeloma, which I believe best explains the clinical picture and symptoms. Severe anemia is almost always associated with multiple myeloma, although rarely there may be a polycythemia. The caprices of multiple myeloma are almost too numerous to mention. The indexes apparently show a macrocytic anemia. If one takes into consideration the deviation of the red-cell count by + or − 13 per cent the mean corpuscular volume can easily be made to appear normal or to appear even larger. Unless large cells were seen on the smear, about which I have no knowledge, I should not accept those indexes as demonstrating a macrocytic type of anemia. One stool guaiac test was negative, so that bleeding probably was not the cause of the anemia. Other stool guaiac tests would have had to be done to establish that. If bleeding was the cause of the anemia and the bone marrow was normal, I should expect an elevated reticulocyte count. The reticulocyte count actually was depressed, indicating to me that the bone marrow was not responding to its major stimulus—anoxia. With a hemoglobin level of 5.2 gm. per 100 cc. there was considerable anoxia, and yet there was apparently no response of the bone marrow to production or release of cells. Anemia in myeloma has been found to be, as in malignant lymphomas, caused in part by a hemolytic process; in other words, in the presence of myeloma cells, there is not only a replacement of the bone marrow but also a decreased red-cell survival time in the peripheral blood. Whether this decreased red-cell survival time is the result of a factor in the serum or in the red cells is not known at the present time.

The white-cell count was decreased somewhat, which is perfectly consistent. The alkaline phosphatase was low. For many years, in this hospital, a low alkaline phosphatase has been considered more indicative of myeloma than a normal or elevated alkaline phosphatase. In series of patients described elsewhere elevated alkaline phosphatase levels have occurred with diffuse multiple myeloma, so that this, like almost any test, cannot be used as a single diagnostic indication of the presence of disease.

Bence-Jones protein, which is a major manifestation of multiple myeloma, was not demonstrated in this patient. On two occasions examination for Bence-Jones protein was negative. If Bence-Jones protein is not looked for by Dr. Jacobson's technic it can be missed.

DR. COHEN: That method was used in this case.

DR. BAKER: I shall have to say that there was no Bence-Jones protein in this case. Then I shall have to say that perhaps Bence-Jones protein either was truly absent or was not going through the kidneys. Bence-Jones protein is of low molecular weight and in the presence of elevated serum proteins attaches itself to the serum proteins and usually does not filter through the kidney. Another point, which was recently brought to my attention, is that the synthesis rate of Bence-Jones protein is many times that of myeloma protein, indicating that Bence-Jones protein is probably not broken off from myeloma protein.[2] The absence of change in the protein in the peripheral blood by the Howe fractionation technic is not unusual. The abnormal proteins that occur in myeloma are frequently precipitated with the albumin fraction; the electrophoretic pattern is about the only means of establishing the presence of these abnormal proteins.

I believe that this case does fit the picture of myeloma, probably multiple. We do not believe that solitary myeloma per se exists as a disease; if myeloma is solitary, it is solitary for a period of years and then becomes multiple. I should make a diagnosis of multiple myeloma, perhaps in a solitary phase, and probably myelomatous kidney disease to explain the phenolsulfonphthalein test.

DR. MARIAN W. ROPES: I always wonder how one can tell what the kidney lesions are and whether or not there are amyloid kidneys or myeloma kidneys in any particular case.

DR. BAKER: I thought about that in this case. I do not know how to distinguish between amyloid kidney and myeloma kidney. Amyloid appears in a high percentage of myeloma. I asked this morning whether phenolsulfonphthalein could possibly be taken up by amyloid deposits. I looked for that information in the literature, thinking that dye might be taken up much as Congo red is.

DR. ROPES: I do not think there is any indication that it is. There is no way of proving which was present; the clinical picture and the laboratory findings are very similar in the two types of renal diseases.

DR. BAKER: Phenolsulfonphthalein tests have also been done on patients with severe amyloid disease, and some of them have been normal.

DR. ROPES: That is correct.

DR. COHEN: In myeloma the amyloid tends to be deposited in striated muscle and in areas characteristically associated with primary amyloidosis. The amyloid deposits are usually not the cause of the proteinuria in multiple myeloma.

DR. ROPES: They may be, but ordinarily they are not.

CLINICAL DIAGNOSIS

?Carcinoma of lung.

DR. WILLIAM H. BAKER'S DIAGNOSIS

Multiple myeloma.

ANATOMICAL DIAGNOSIS

Multiple myeloma.

PATHOLOGICAL DISCUSSION

DR. COHEN: As Dr. Baker suggested, this was a case of plasma-cell myeloma. The biopsy taken from the mass in the rib was composed almost entirely of

FIGURE 3.

sheets of tightly packed, mature plasma cells with occasional immature forms. Unfortunately, no further clinical studies were undertaken. The patient was given urethane, but the anemia was progressive, as was a rapidly developing uremia. He died a few weeks after the biopsy. The nonprotein nitrogen went from 38 to 208 mg. per 100 cc. in a period of several weeks.

At post-mortem examination interesting findings were present in the bones and kidneys. The bone-marrow cavities of the ribs, vertebras and skull were occupied by hemorrhagic, jellylike material characteristic of myelomatous tissue. Replacement of the marrow by tumor was certainly in part responsible for the anemia. The kidneys were pale, granular and somewhat decreased in size. Histologically, they presented lesions that are considered to be characteristic of the kidney in multiple myeloma and are responsible for the frequent occurrence of a rapidly developing uremia in this condition. This lesion consists of a deposition of protein casts that extend along the length of the tubules and obstruct them (Fig 3). In relation to these casts there are frequent inflammatory infiltrates consisting of polymorphonuclear leukocytes and lymphocytes. Around the casts syncytial giant cells form. These are apparently a reaction of the tubular epithelium to some constituent of the cast. Occasionally, there is calcification in the casts and in the interstitium of the kidney. Although foci of myeloma are occasionally found in the kidney the term "myeloma kidney" refers to the histopathologic picture just described, and the tumor, as a rule, is not present.

Factors that influence the formation of casts in kidney tubules are numerous, and complex physicochemical relations are involved. In myeloma, cast formation is not well correlated with proteinuria or the level of serum protein. It is probable that qualitative as well as quantitative changes contribute to the production of the casts.

I believe that Dr. DuToit has some information about the proteins in this case.

DR. CHARLES H. DUTOIT: Recently, by use of paper electrophoresis, it has been possible to study the protein abnormalities in these patients with much greater precision. The abnormal proteins found in multiple myeloma have attracted a great deal of interest since Bence-Jones,[3] in 1848, first described the urinary protein that bears his name. Later, Ellinger[4] described the elevated serum proteins, usually in the so-called globulin fraction, that certain cases of this disease present. Methods of studying these abnormal proteins remained crude until recently. Jacobson and Milner[5] pointed out how difficult accurate identification of Bence-Jones protein in the urine can be. In the light of present knowledge it would not be surprising if an occasional patient with multiple myeloma excreted a protein in the urine that did not have the classic solubility characteristics described by Bence-Jones.

The relation between the urine and serum proteins in myeloma is far from clear. Those showing the high globulin do not necessarily have Bence-Jones protein in the urine. In fact there is a suggestion of an inverse correlation between the two abnormalities. It has been speculated that differences in the serum protein from case to case determine whether it will build up in the serum or be rapidly excreted in the urine. However, recent work indicates fundamental differences between the serum and urinary proteins even when they occur in the same patient.[2,6]

These slides (Fig. 4 and 5) demonstrate the electrophoretic pattern of the serum, urinary and pleural proteins in this patient and the pattern of a normal serum protein and of a urinary protein from a patient with nephrosis. In this particular case, unlike most, electrophoresis was of special value because there is an abnormality that is not apparent from the total protein determination or usual albumin and globulin separation. The abnormal feature of the serum pattern is a fairly discrete, sharply circumscribed spot in the gamma-globulin area. This is a typical example

of what Gutman[7] has called the M protein abnormality. The discreteness of this spot, not its relative position, is quite characteristic of multiple myeloma. Other diseases characterized by hyperglobulinemia, such as cirrhosis of the liver and sarcoid, produce a diffuse enlargement of the entire gamma-globulin region quite unlike this picture.

The electrophoretic pattern of the urine is similar to that of the serum. Again, we see a highly abnormal discrete protein spot in the gamma-globulin area. One of the possible reasons for difficulty in demonstrating Bence-Jones protein in this urine is also apparent. Other urinary proteins are present, especially albumin. These would mask the solubility of Bence-Jones protein at the boiling point.

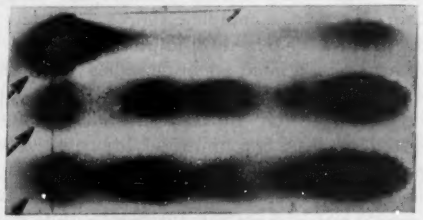

FIGURE 4. *Electrophoretic Pattern of Protein in the Urine, Serum and Pleural Fluid.*
Arrows point to the characteristic abnormal spot in gamma-globulin area in each pattern.

The bottom pattern is the pleural effusion, which is very similar to the serum.

The protein anomalies in serum or urine may be totally absent in multiple myeloma. At present we are not able to state with certainty that these changes in serum or urine or both are absolutely diagnostic of multiple myeloma. We have 2 cases with striking serum protein anomalies of this type that have been tentatively labeled monocytic leukemia and lymphoma. However, myeloma cannot be completely excluded.

DR. BENJAMIN CASTLEMAN: Do you mean to say that, when you see such a pattern in the serum, the patient has multiple myeloma?

DR. DUTOIT: The relative electrophoretic mobility of the abnormal protein varies considerably from case to case. The discrete appearance of the abnormal spot is the characteristic finding.

DR. CASTLEMAN: The pattern of the protein in the urine is not the same?

DR. DUTOIT: That is true. The electrophoretic mobilities of the abnormal urinary and serum proteins are usually not quite the same.

FIGURE 5. *Electrophoretic Pattern of Normal Protein in the Serum and of Protein in the Urine from a Patient with Nephrosis for Comparison.*

The discreteness of the spot in the urine, again, is the distinctive characteristic.

DR. CASTLEMAN: Does that spot always represent Bence-Jones protein?

DR. DUTOIT: In this case I cannot say. The physicians assure me that they ran through all Dr. Jacobson's 39 steps and still could not conclusively demonstrate Bence-Jones protein. However, the general appearance of this electrophoretic pattern is strikingly similar to that of 2 or 3 others in which Bence-Jones protein has been demonstrated.

The electrophoretic pattern of urinary proteins in other diseases usually bears a closer resemblance to the serum pattern.

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"OF PUBLISHING SCIENTIFIC PAPERS"

BAD writing, according to the familiar aphorism, serves no purpose that cannot be better served by good writing. The thesis applies not only to technics in writing; it can be expanded to include methods, material and motives.

In some two-score pungent paragraphs, employing also the graphic arts in the form of cartoons, Dr. George E. Burch, Henderson Professor of Medicine at Tulane University School of Medicine, has set up a series of guides for author, reader, critic and editor that indicate right paths by warning against wrong ones. These crystallized concentrates comprise, in their aggregate, a complete short essay under the title "Of Publishing Scientific Papers."*

Describing a good scientific paper as one that "contains new data well oriented among those already in the literature," Dr. Burch points out that the purpose of the investigation must be indicated, the experiments described and the origin of the ideas precisely presented. The results must then be summarized "clearly but without modification, selection, or elimination of data for the purpose of reaching preconceived, prejudiced or apparently acceptable conclusions." Although the investigator and author is primarily responsible for the quality of the paper, others such as the "benefactor" or sponsor (if any), the institution, the editor and the publisher, all of whom are concerned with its production, must accept their share of the final responsibility.

The essayist heads his blacklist of undesirable characters with the self-plagiarist, a calculating and unfortunately ubiquitous writer who draws freely on his own previous publications for each new paper, continually watering his original porridge into the thinnest of gruels. His bibliography may refer largely to his own published material, and he also quotes from his earlier papers without benefit of quotation marks, but without failing to credit himself with the ideas expressed. Like the self-aggrandizer and the obsessive or quantitative writer, the self-plagiarist, were the recommendations of the Lord High Executioner put into effect, never would be missed.

Dr. Burch has a word or two to say about the responsibilities of the university and other sponsors of research in not prodding for premature publication or using too much the yardstick of publication as the criterion of scientific accomplishment. Likewise the editor and the editorial board, into whose hands is given the selection of papers to be published, should have qualifications that include (so far as possible) "scientific knowledge, irreproachable scientific interest, objectivity, industry, critical judgment and ability to write scientifically themselves."

Their interest is genuinely that of good scientific and clinical medicine and the prestige of the journal that they represent. Personal publicity is entirely foreign to the anonymous services that they perform.

*Burch, G. E. *Of Publishing Scientific Papers.* 40 pp. New York: Grune & Stratton, 1954.

THE PEACETIME VETERAN

EVEN in such rousing times of peace as those that have existed since February 1, 1955, veterans who knew not the conflicts of the past will still be entitled to certain not inconsiderable benefits in the future. These benefits are outlined in the same release from the Veterans Administration that declares all persons entering the armed forces for the first time on and after that date to be peacetime veterans when they leave the service of their country. As such they will be ineligible for any of the benefits provided by the Korean G I Bill or for other benefits payable to veterans of that period of conflict.

Lest these veterans should consider themselves to be forgotten and neglected by an ungrateful republic, however, the benefits to which they are entitled are listed and described in some detail. The only stipulations regarding eligibility are that for certain types of insurance coverage the veteran must have been thirty-one days in active service, and that for any and all benefits discharge, if not necessarily honorable, must at least have been under other than dishonorable conditions.

As regards medical and dental care the peacetime veteran who was severed from the service without dishonor may be entitled to hospitalization, outpatient medical and dental treatment and prosthetic service for a service-connected disability. He may furthermore receive domiciliary care if he is incapacitated from earning a living and has no adequate means of support. Such support, however, may be at least partially provided by disability compensation ranging from $14 to a maximum of $336 a month unless the disability resulted from such extra-hazardous service as simulated warfare, in which case wartime rates may be applied, up to a maximum of $420 monthly.

Blindness in eligible peacetime veterans entitles those who are receiving compensation for service-connected disabilities to special consideration even where the blindness itself is not service-connected. These considerations include electronic and mechanical equipment, seeing-eye dogs, the training of the veteran in the use of the dog and medical attention for the dog. Veterans entitled to compensation for permanent and total service-connected disability for the loss or loss of use of both legs are entitled to grants for special "wheel-chair" homes, whether newly built, bought or remodeled. Such grants are not to exceed 50 per cent of the cost of the home, up to a maximum of $10,000. Various types of life insurance and indemnity are available for peacetime veterans as they were for those who incurred the risks of war.

And finally, when the veteran compensated for disability incurred in line of duty reaches the end of his line, he will be buried by his country, to the limit of $150, in a casket draped with an American flag, which will be issued, on application, by Veterans Administration field offices, the majority of first, second and third class post offices and those fourth class offices that are located in county seats. Nor does the solicitude end here, for if the veteran's death can justly be attributed to his service, compensation will be extended to his widow, children and dependent parents.

E PLURIBUS UNUM

EVERYONE will rejoice that last year the 100,000 victims of poliomyelitis in this country benefited to the extent of approximately $50,000,000 through the March of Dimes campaign. This amounted to a contribution of about 30 cents from every man, woman and child in the United States.

A number of other causes are worthy of at least equal support. There are in the nation 200,000 victims of muscular dystrophy, 250,000 with multiple sclerosis, 400,000 with tuberculosis, 600,000 with cerebral palsy, 700,000 with cancer, 2,500,000 with mental disease (under treatment alone), 7,500,000 with arthritis and rheumatism and well over 16,000,000 with heart disease (which alone causes 8,000,000 deaths each year). No fund campaign for the benefit of any of these groups has succeeded in collecting half as much as the March of Dimes.

On a purely arithmetical basis it seems that if one gave 30 cents to poliomyelitis one should have given 60 cents to muscular dystrophy, 75 cents to multiple sclerosis, $1.20 for tuberculosis control, $1.80 to cerebral palsy, $2.10 to cancer, $7.50 to mental disease, $22.50 to arthritis and rheumatism, and $48.00 to heart disease.

Actually, the mythical average citizen gave only 8 cents to the campaign against heart disease, — a fourth as much as he gave to the March of Dimes, — 14 cents toward cancer eradication, 15 cents for Christmas seals (tuberculosis) and about 1¼ cents to multiple sclerosis. Other campaigns fared no better. The same average citizen spent at least $30 for cigarettes. Is 1 cent for poliomyelitis and $1 for cigarettes the measure of one's regard for others as compared to one's concern for himself?

Incidentally, those who believe that there are too many of these campaigns and that they should be united under the aegis of the United Community Services should remember that the needs of the special disease foundations are conservatively estimated at $130,000,000 annually. Red Feather campaigns collected last year all over the country only about $287,000,000 and would have to increase their budgets by nearly 50 per cent to take care of this added burden. One can easily understand why the sponsors of special fund campaigns prefer to go it alone, rather than to accept overenthusiastically the motto of the United States, so gracefully expressed by three words in Latin.

PUBLICATIONS OF TUFTS-NEW ENGLAND MEDICAL CENTER

UNDER the initial editorship of Miss Blossom Appel, of the Class of 1956, Tufts College Medical School, the *Tufts Medical Journal* and the *Bulletin of the New England Medical Center* have combined to appear hereafter as the pocket-sized *Bulletin of Tufts-New England Medical Center.* In its joint capacity the new bulletin will give suitable publicity to the activities of the School, the Pratt Diagnostic Clinic, the New England Center Hospital, the Boston Dispensary and the Boston Floating Hospital. It will also provide a medium for the publication of clinical and scientific papers contributed by members of the faculty of the School and of the staffs of the hospitals.

As is stated editorially in its first quarterly number, now current, the new bulletin is a combined graduate and undergraduate publication, eliminating the duplication of material at the same time that it stimulates greater productivity. Although largely staffed from the undergraduate group the *Bulletin* has the assistance of a faculty staff and advisers.

Nearly synchronously with the appearance of the *Bulletin* the first copy of the revised *New England Medical Center News,* Number 1 of Volume VII, for March and April, 1955, has gone into the mail. The *News* serves the same institutions as the *Bulletin,* with Tufts College Dental School in addition.

Extirpation of the Uterus. — *We have received a letter from Dr. Walter Burnham, of Lowell, in which he claims to have successfully performed the operation of extirpation of the uterus, together with both the ovaries, through the abdominal parietes, in that city, June 25th, 1853 . . .*

Boston M. & S. J., *May 10, 1855*

MASSACHUSETTS MEDICAL SOCIETY

STATED MEETING OF THE COUNCIL

A stated meeting of the Council will be held in the Georgian Room, Hotel Statler, Boston, on Monday, May 16, at 5 p.m.

Business:

1. Call to order at 5 p.m.
2. Presentation of record of meeting held February 2, 1955, as published in Vol. 252, Supplement No. 1, March 17, 1955, of the *New England Journal of Medicine.*
3. Reports of standing and special committees.
4. Such other business as may legally come before this meeting.

ROBERT W. BUCK, M.D.,
Secretary

SCHOOLS OF GRADUATION

A recent check of the schools from which fellows of the Society hold degrees shows that of every 100 members, 33 graduated from Tufts, 24 from Harvard, 11 from Boston University, 14 from other existing approved schools, 14 from discontinued or unapproved medical schools and 4 from foreign universities.

It will probably be possible to indicate, in the next edition of the *Directory,* the school of graduation of each member and, if the fellows do not object, board certification or other evidence of special qualification.

ROBERT W. BUCK, M.D.
Secretary

DEATH

CHATIGNY — Joseph V. Chatigny, M.D., of Taunton, died on March 24. He was in his sixty-fifth year.

Dr. Chatigny received his degree from the College of Physicians and Surgeons, Boston, in 1916. He was formerly president of the Morton Hospital staff, Bristol North District Medical Society and the Taunton Doctors' Club and was school physician. He was a member of the New England Obstetrical and Gynecological Society and the New England Society of Psychiatry and a fellow of the American Medical Association.

He is survived by his widow, two sons, a sister, a brother and five grandchildren.

CORRESPONDENCE

QUARTERLY JOURNAL OF MEDICINE

To the Editor: The editorial, "S. G. and O., 1905-," in the March 24 issue of the *Journal,* reciting the distinguished background of *Surgery, Gynecology and Obstetrics,* recalls the parallel story of the *Quarterly Journal of Medicine,* as related in Cushing's *Life of Sir William Osler.*

A group of distinguished British clinicians, including Drs. Wilmot Herringham, A. E. Garrod, William Hale-White, S. D. Rolleston, J. Rose Bradford and Robert Hutchison, fostered such a project and invited Osler to meet with them at the home of Herringham on May 23, 1906. On this occasion, Osler asked, "Why not form a National Association of Physicians first and let the Journal come to be its official organ?" In the discussion that followed, he suggested that the Oxford University Press might be induced to enter the field of medical publications. As an outgrowth of this suggestion, the Association of Physicians of Great Britain and Ireland was founded, and the *Quarterly Journal of Medicine* became its official medium, published by Oxford University Press. Until his death twelve years later, Sir William was one of the editors.

By this singular train of circumstances, the Association of Physicians of Great Britain and Ireland is, in truth, a daughter of the Association of American Physicians, a relation of which we may be justly proud.

WILLIAM S. MIDDLETON, M.D.
Chief Medical Director
Department of Medicine and Surgery
Veterans Administration
Washington, D.C.

CORTISONE TREATMENT OF ACUTE HEMORRHAGIC PANCREATITIS

To the Editor: The case report in the March 24 issue of the *Journal,* "Acute Hemorrhagic Pancreatitis: Treatment with cortisone," contains interesting data regarding the beneficial effects of cortisone in pancreatitis. However, the report does not state whether standard therapeutic measures

for pancreatitis were also instituted, particularly gastric suction and anticholinergic agents to diminish gastric and pancreatic secretion. Unless this well established plan of management was followed, the comparative benefits of adrenocorticosteroid therapy are difficult to assess.

In the present stage of knowledge, the readers of the *Journal* certainly should not be influenced in favor of the substitution of cortisone or similar agents for the usual therapeutic handling of pancreatitis, although they may be cautiously tried as therapeutic adjuncts.

The authors of this report also state, "A review of the American literature to date has failed to reveal any report of acute pancreatitis treated by either cortisone or ACTH." It should be brought to the attention of the authors that an article appeared in the August, 1952, issue of the *Archives of Surgery*, entitled "Acute Hemorrhagic Pancreatitis: Report of case with cortisone treatment," by Stephenson, Pfeffer and Saypol. The same paper was subsequently abstracted in the November 29, 1952, issue of the *Journal of the American Medical Association*. In addition the use of ACTH in pancreatitis was discussed by Berk in his paper, "Management of Acute Pancreatitis," in the May 2, 1953, issue of the *Journal of the American Medical Association*.

EDGAR ROSEN, M.D.

Oakland, California

Dr. Rosen's letter was submitted to one of the authors of the paper in question, who offers the following reply:

To the Editor: I am glad that Dr. Rosen was able to point out an additional reference to the use of cortisone in the treatment of this disease.

Our patient received neither anticholinergic drugs nor gastric suction. I doubt if this type of therapy is as well established as Dr. Rosen assumes.

We fail to see how gastric suction could have any beneficial effect upon a hemorrhagic lesion in the pancreas.

Our case was reported in the firm belief that cortisone will prove to be the definitive type of therapy for the treatment of acute hemorrhagic pancreatitis.

Thank you for the opportunity of replying to Doctor Rosen's letter.

IRVING S. ESKWITH, M.D.

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

Clinical Orthopaedics. Edited by Anthony F. DePalma, with the assistance of the associate editors and the board of advisory editors. No. 3. 4°, cloth, 230 pp., with illustrations. Philadelphia: J. B. Lippincott Company, 1954. $7.50.

This new volume in an important series contains a large number of articles dealing with soft-tissue conditions around the joints and with general orthopedic conditions. Lists of references are appended to the papers; there is a good index, and the publishing is excellent. The series is recommended to all medical libraries and to orthopedists.

The Manual of Antibiotics, 1954-1955. Preparations, Therapeutic Index, Generic and Trade Names, Producers. Edited by Henry Welch, Ph.D. 4°, cloth, 87 pp. New York: Medical Encyclopedia, Incorporated, 1954. $2.50.

This manual constitutes a valuable listing of antibiotic preparations.

NONCLINICAL NOTES

PRESIDENT OF THE BLUE SHIELD COMMISSION

Dr. Norman A. Welch, of Boston, was recently elected president of the Blue Shield Commission, national co-ordinating agency of the Blue Shield Plans in the United States, Puerto Rico, Canada and Hawaii.

BIGELOW MEDAL

Dr. Edward D. Churchill, John Homans Professor of Surgery at the Harvard Medical School and chief of surgical services of the Massachusetts General Hospital, became on April 11 the thirteenth recipient of the Bigelow Medal of the Boston Surgical Society.

Dr. Henry Jacob Bigelow, for whom the award was named, was professor of surgery at Harvard from 1849 to 1882.

NOTICES

NEW ENGLAND RHEUMATISM SOCIETY

The spring meeting of the New England Rheumatism Society will be held in Stearns Auditorium, New England Medical Center, on Friday, May 20, at 8 p.m.

The program is as follows:

Metabolic and Clinical Studies of Metacorten (Metacortandracin). Evan Calkins, Leon Resnick and Walter Bauer.

Psychiatric Problems in Rheumatoid Children. Gaston Blom.

An Analysis of Two Hundred Cases of Gout. Heinrich G. Brugsch, Michael Pierek and Jacob Yules.

Juxto-articular Bone Cysts Associated with Rheumatoid Arthritis. J. L. Sosman and W. Bardawil.

NEW YORK STATE DEPARTMENT OF HEALTH

A position is available for a public-health physician who has specialized in the diagnosis and treatment of tuberculosis, including the interpretation of x-ray films of the chest, with the New York State Department of Health. The beginning salary is $10,470. Further information may be obtained from Richard H. Mattox, Director, Office of Personnel Administration, New York State Department of Health, State Office Building, Albany 1, New York.

ACADEMY–INTERNATIONAL OF MEDICINE MOTION-PICTURE FILMS

A completely revised fourth edition of *Professional Films* is being compiled, containing biographic data on authors of motion-picture films and information on the audiovisual activities of medical and dental schools and graduate teaching centers.

In order that they may be included, film authors are requested to write for questionnaires to the Academy-International of Medicine, 601 Louisiana Street, Lawrence, Kansas.

SOCIETY MEETINGS AND CONFERENCES

MAY. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.

MAY 5–26. Consultation Clinics for Crippled Children in Massachusetts. Page 733, issue of April 28.

MAY 6–8. Student American Medical Association. Page 461, issue of March 17.

MAY 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.

MAY 10–26. Boston City Hospital House Officers' Lectures. Page 509, issue of March 24.

MAY 10. Harvard Medical Society. Page 741, issue of April 28.

MAY 11. New England Pediatric Society. Page 741, issue of April 28.

MAY 11–25. Lahey Clinic Lectures. Page 289, issue of March 17.

MAY 13 and 14. American Association for Cleft Palate Rehabilitation. Page 461, issue of March 17.

MAY 13–15. American Academy of Dental Medicine. Page 554, issue of March 31.

MAY 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston. Program. Pages 734-738, issue of April 28.

MAY 18–JUNE 15. Boston State Hospital. Psychiatry Seminars. Page 461, issue of March 17.

MAY 18–20. American College of Cardiology. Page 414, issue of March 10.

MAY 20. New England Rheumatism Society. Notice above.

MAY 23–27. American Trudeau Society. Page 462, issue of March 17.

MAY 29–JUNE 2. American Society of X-Ray Technicians. Page 553, issue of March 31.

JUNE 1–4. American Proctologic Society. Page 648, issue of April 14.

JUNE 1–5. American College of Chest Physicians. Page 553, issue of March 31.

JUNE 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.

JUNE 6–10. Woman's Auxiliary to the American Medical Association. Page 647, issue of April 14.
JUNE 7–9. United States Public Health Service Medical-Officer Examinations. Page 509, issue of March 24.
JUNE 10–12. American Electroencephalographic Society. Page 647, issue of April 14.
JUNE 13–15. American Neurological Association. Page 689, issue of April 21.
JUNE 13–17. European Rheumatology Congress. Page 742, issue of April 28.
JUNE 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.
JULY, AUGUST and SEPTEMBER. Beth Israel Hospital Course. Page 509, issue of March 24.
JULY 10–16. Congress of Nobel Prize Winners. Page 510, issue of March 24.
JULY 11–15. Symposium on Tuberculosis. Page 509, issue of March 24.
AUGUST 28–SEPTEMBER 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
OCTOBER 6–8. Academy of Psychosomatic Medicine. Page 509, issue of March 24.
OCTOBER 22–26. American Heart Association. Scientific Session. Page 603, issue of April 7.
OCTOBER 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
NOVEMBER 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
NOVEMBER 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
NOVEMBER 29–DECEMBER 2. Interim Session of the American Medical Association. Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, MAY 12

THURSDAY, MAY 12

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Thoracic Conference. Medical Management during Cardiac Surgery. Drs. Harrison Black and Harold T. Mankin. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
5:00 p.m. Case Presentation and Pathological Discussion Followed by a Subject of Special Presentation. Joslin Auditorium, New England Deaconess Hospital.

FRIDAY, MAY 13

American Association for Cleft Palate Rehabilitation. Hotel Statler, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

SATURDAY, MAY 14

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Anesthesia Conference. Dr. Etsten. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*9:00–10:30 a.m. Surgical Grand Rounds. Dr. Child and Staff. Stearns Auditorium, New England Center Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*10:30 a.m.–12:00 m. Surgical History Meeting. Stearns Auditorium, New England Center Hospital.
*11:00 a.m.–12:00 m. Hematology Clinic. Dr. William Dameshek. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.

MONDAY, MAY 16

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Medical-Surgical Rounds. Drs. Baty and Swenson. Pratt Lecture Hall, Joseph H. Pratt Diagnostic Hospital.
*12:00 m.–1:00 p.m. Metabolism Conference. Dr. Schwartz. Stearns Auditorium, New England Center Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:00 p.m. Surgical Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Theories of Narcosis. Dr. Vandam. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.
*7:00–9:00 p.m. Slide Seminar in Pathology. Dr. MacMahon. Stearns Auditorium, New England Center Hospital.

TUESDAY, MAY 17

Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
*8:00 a.m. Combined Rounds. Children's Hospital, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00 a.m. Geriatrics Clinic. Peter Bent Brigham Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic, New England Deaconess Hospital.
*4:30–6:00 p.m. Anesthesia Conference. Dr. Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting followed by Clinical Conference (Medical, Surgical, Obstetrical). Faulkner Hospital.
*7:00 p.m. Boston City Hospital House Officers' Lecture. Simple Goiter. Dr. E. B. Astwood. New Cheever Amphitheater, Dowling Building, Boston City Hospital.

WEDNESDAY, MAY 18

Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Boston State Hospital Psychiatry Seminar. The Danger of Suicide. Dr. William F. Murphy. Reception Building Auditorium, 591 Morton Street, Dorchester.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Neurology, Neurosurgery and Psychiatry. Drs. Sullivan, B. Selverstone and Hope. Stearns Auditorium, New England Center Hospital.
*12:00 m.–1:00 p.m. Clinicopathological Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Management of the Leukemic Patient. Dr. John W. Norcross. The Bleeding Dyscrasias. Dr. Donat Cyr. Joslin Auditorium, New England Deaconess Hospital.

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1. Suarez-Murias, E. L.: Internat. Rec. Med. *166*:475 (Nov.) 1953. 2. Rees, L.: J. Ment. Sc. 99:62 (Jan.) 1953. 3. Morton, J. H., et al.: Am. J. Obst. & Gynec. *65*:1182 (June) 1953. 4. Morton, J. H.: Internat. Rec. Med. *166*:505 (Nov.) 1953.

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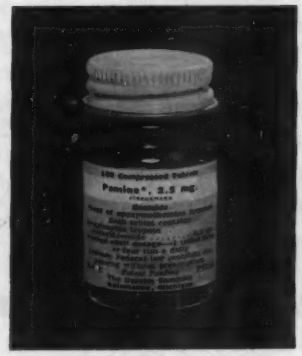

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1. Rukes, J. M., et al.: Metabolism 3:481, 1954.
2. Peterkin, G. A. G.: Brit. M. J. 1:522, 1954.

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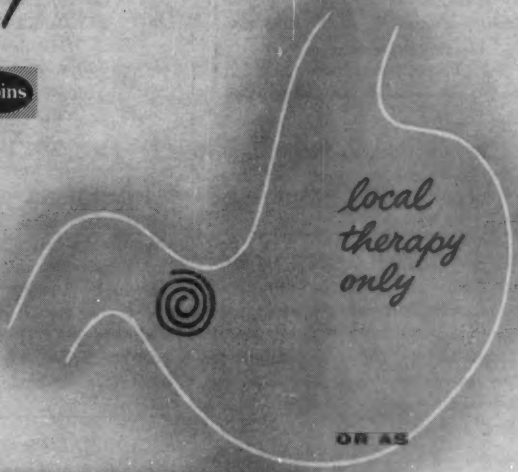

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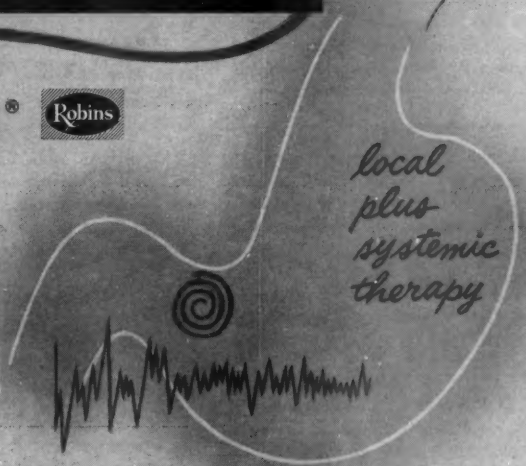

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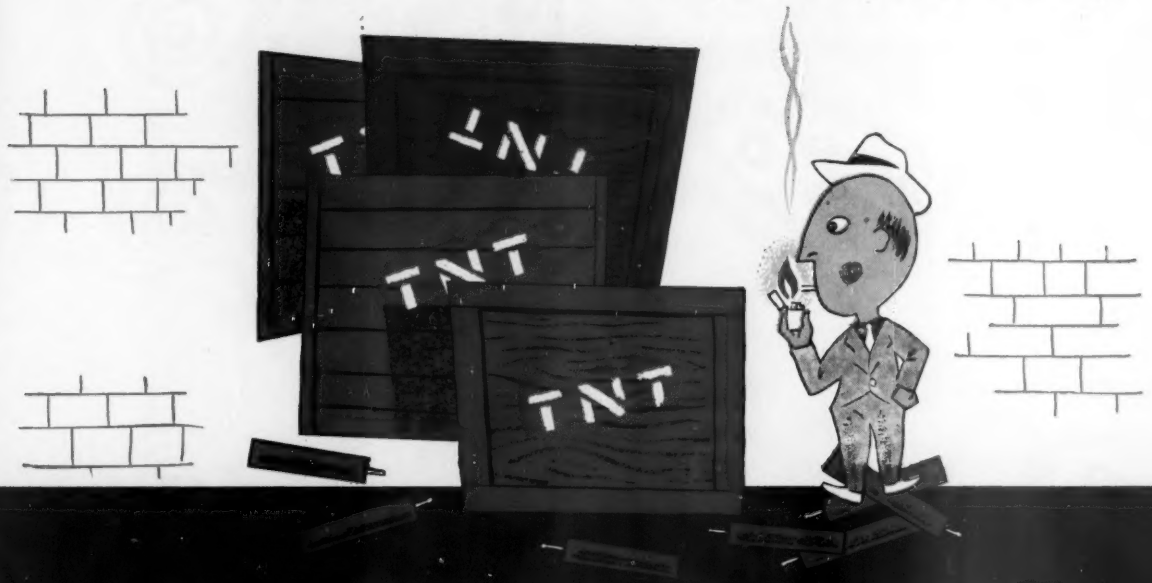

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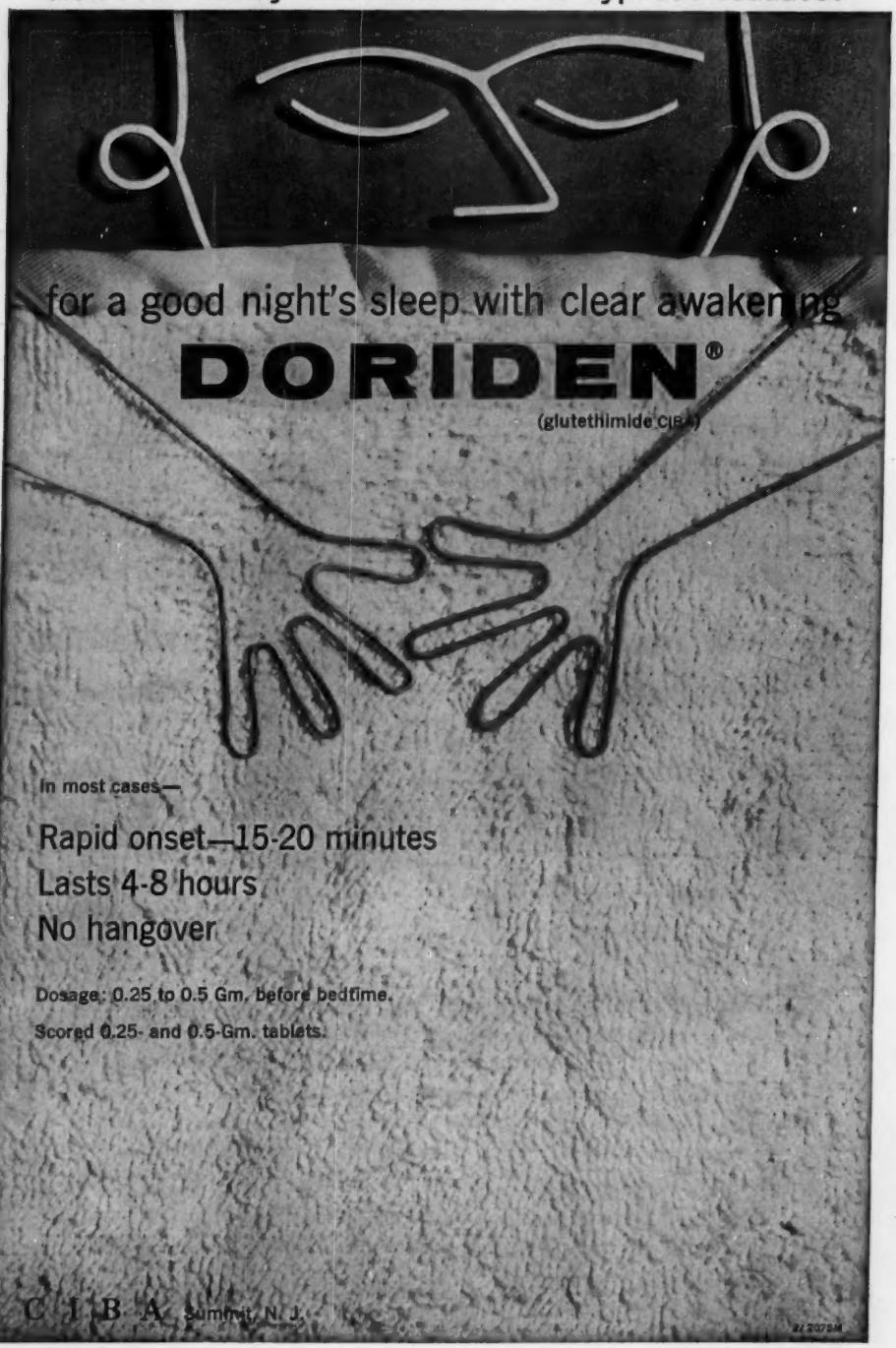
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